Supporting cancer patients in managing distress

Admiraal, Jolien

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SUPPORTING CANCER PATIENTS IN MANAGING DISTRESS

New insights in the use of the Distress Thermometer &
Problem List and effects of web-based support programs

Jolien Admiraal

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Promotores

Prof. dr. A.K.L. Reyners

Dr. C.P. Schröder

Copromotor

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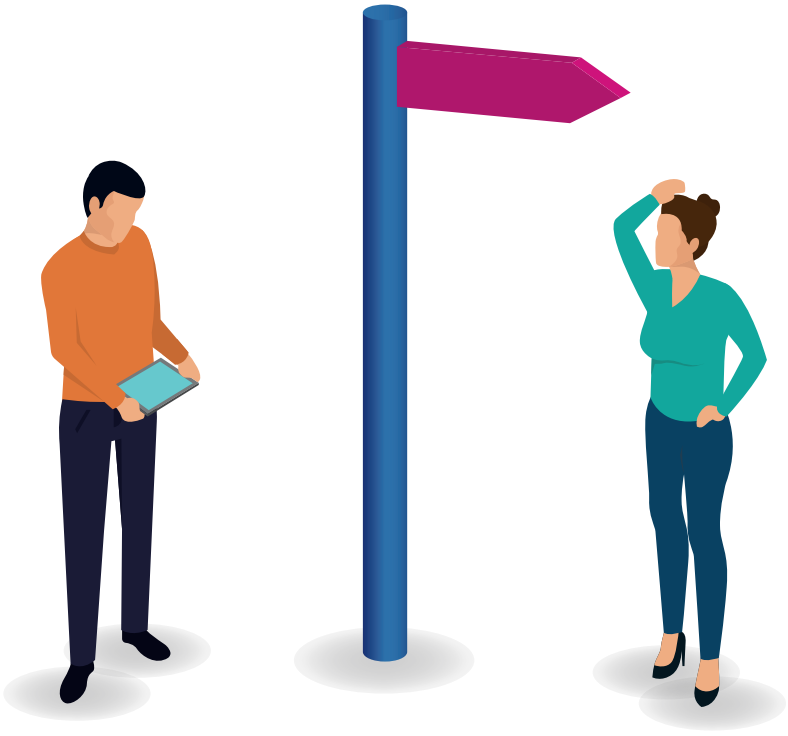

CHAPTER 1

General introduction

INTRODUCTION

Cancer is currently the leading cause of death worldwide, causing over 8 million deaths in 2012 [1]. In the Netherlands, about 1 out of three women and 1 out of two men receive a diagnosis of cancer at some point in their life [2]. Due to improved detection, an ageing population and an increase in risk factors (e.g. tobacco use, unhealthy diet and physical inactivity) the incidence of cancer is expected to increase during the coming decades [1,2]. Luckily, survival increases as well because of improved cancer detection and treatment [2]. Many cancers are curable if detected early and treated adequately.

In the majority of the chapters within this thesis, the focus is on cancer patients in general, irrespective of cancer type and stage. In two chapters, studies are being described in which only patients with breast cancer participate. The patients who are enrolled in these studies are patients with breast cancer treated with curative intent.

Breast cancer is the most prevalent cancer in women worldwide [3]. The lifetime risk of being diagnosed with breast cancer in the Netherlands is about 1 in 7 (invasive cancer and pre-cancer stage (DCIS) [2,4]). The incidence is expected to increase during the coming years [5]. Next to better detection and an ageing population, risk factors for breast cancer such as having no/few children or having a first child after the age of 30, no or short breastfeeding, being overweight (after menopause), high alcohol consumption and a lack of physical exercise changed in an unfavorable direction during the last years [5]. The survival rate of breast cancer is relatively high and is expected to further increase. In 2012, the five-year survival rate of breast cancer was 87% compared to 62% across all primary cancer sites [2].

Psychosocial impact of cancer diagnosis and treatment

Receiving a diagnosis of cancer and undergoing (different types of) treatment (Box 1) poses major challenges to patients' coping abilities. Coping has been defined as the way an individual deals with a stressor (e.g. cancer). Coping strategies can be active (trying to change the stressor itself) or passive (change how one relates to the stressor). According to the transactional model of stress and coping of Lazarus and Folkman (1984), coping depends on how one appraises a stressor. When encountering a stressor, an individual primarily appraises the stressor as either threatening or non-threatening, and secondarily in terms of whether one has the resources to cope with the stressor effectively (figure 1). Well-being deteriorates when an individual appraises that the demands of the stressor exceed personal resources [6].

Box 1. Cancer treatment – a quick glance

After being diagnosed with cancer, treatment will be administered with a curative (to cure the illness) or palliative intent (to relieve symptoms, to improve quality of life and/or to prolong life). Several treatment modalities can be used to treat cancer, depending on the type of cancer, the characteristics of the tumor, the preferences and fitness of the patient. The following treatment modalities can be administered either alone or in combination:

Surgery. Most patients with cancer will receive some type of surgery. Surgery can be used to diagnose, treat and/or to prevent cancer. If cancer has not spread to other parts of the body, surgery provides the best chance for cure. Concerning breast cancer, part of the breast that contains the malignancy (lumpectomy) or the whole breast (mastectomy) can be removed, often in combination with a lymph node examination. The type of surgery depends on tumor-related characteristics and the patient's wishes. Patients can opt for a direct reconstruction of the breast (cosmetic surgery) or decide later on. Side effects that can occur, especially after a lymph node dissection are; pain/numbness, limitations in arm-shoulder function and lymphedema.

Radiotherapy. This therapy uses X-rays or other high-energy particles from linear accelerator machines to destroy or damage cancer cells. The total dose of radiotherapy is usually divided into smaller doses (fractions). Patients with breast cancer may receive up to 22 fractions. The side effects most commonly reported are a loss of energy and skin complaints in the treated area.
Proton therapy is a newer type of radiotherapy that uses protons rather than X-rays to treat cancer. With proton therapy, there is less radiation dose outside of the tumor, possibly resulting in fewer side effects than standard radiotherapy. For breast cancer, proton therapy is only applied when fewer side effects are expected compared to standard radiotherapy.

Systemic therapy. In contrast to surgery and radiotherapy that treat cancer locally, systemic therapy works throughout the whole body.

- *Chemotherapy:* this therapy uses a medicine or drug (cytotoxic drugs) to kill cancer cells. Chemotherapy is usually being administered by an injection or by intravenous infusion and is given in cycles, with rest periods in between. The frequency and length of chemotherapy varies, depending on (among others): the type of cancer, the types of drugs administered, and the expected toxicities of the drugs. Breast cancer patients may receive up to 16 cycles of chemotherapy. Side effects are common with chemotherapy. Most frequent side effects are fatigue, hair loss, nausea, vomiting and bone marrow depression.
- *Targeted therapy:* this therapy is a type of cancer treatment that uses drugs or other substances to more precisely identify and attack cancer cells. Targeted therapy works by targeting the cancer's specific genes, proteins, or the tissue environment that contributes to cancer growth and survival. These genes and proteins are found in cancer cells or in cells related to cancer growth, like blood vessel cells. Examples are monoclonal antibodies such as trastuzumab and pertuzumab administered in breast cancer patients. A substantial part of targeted therapy used in clinical practice is hormonal therapy.
- *Hormonal therapy:* this therapy uses a medicine to block the effects of hormones as some cancers use hormones to grow. Hormonal therapy is frequently used as part of breast cancer treatment, especially when the tumor is sensitive to the female hormones estrogen and/or progesterone and has unfavorable prognostic characteristics. Hormonal therapy is generally given for five years to breast cancer patients who receive curative treatment. The drug is most often taken as a pill on a daily basis (tamoxifen, aromatase inhibitors). The most common side effects are: hot flushes, vaginal dryness, painful joints, mood changes and weight changes.
- *Immunotherapy:* Immunotherapy is a cancer treatment that uses substances made by the body or in a laboratory to improve or restore the immune system function. There are several types of immunotherapy including the administration of cytokines or immune checkpoint inhibitors.

After cancer treatment ends, patients will continue to visit the hospitals for routine follow-up visits. During the follow-up visits, patients will be examined on cancer recurrence and presence of other malignancies. Treatment side-effects and general well-being are also discussed with the patient.

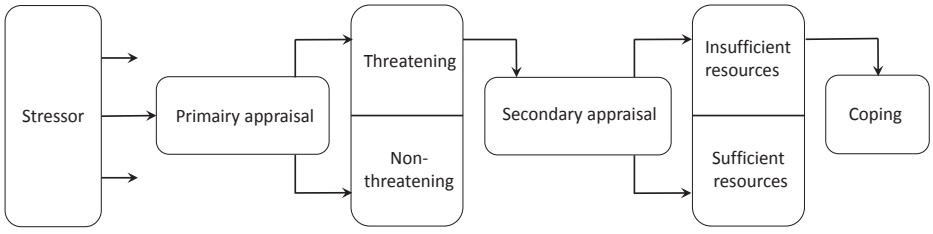

Figure 1. Stress-coping model of Lazarus & Folkman (1984)

The outcome of the appraisal process may elicit a range of emotional reactions in patients. A significant proportion of patients with cancer develop a psychiatric/psychological mood disorder such as depression, anxiety and adjustment disorder at some point in the cancer trajectory. About 30-40% of patients in hospital settings experience one or a combination of these mood disorders [7-10]. Many emotional reactions to a cancer diagnosis and its treatment cannot be captured by any formal psychiatric/psychological diagnosis however [11]. Therefore, the concept of 'distress' has been introduced [12]. Distress has been defined as:

"a multifactorial unpleasant emotional experience of a psychological (cognitive, behavioral, emotional), social, and/or spiritual nature that may interfere with the ability to cope with cancer, its physical symptoms and its treatment. Distress extends along a continuum, ranging from common normal feelings of vulnerability, sadness, and fears, to problems that can become disabling such as depression, anxiety, panic, social isolation and spiritual crisis" [13]

The advantages of the concept of distress is the avoidance of the stigma often tied to psychiatric/psychological diagnoses and the usefulness for both mental and non-mental health care professionals. Moreover, the concept is easy to understand and to report by patients [12,14]. Distress has been associated with reduced health-related quality of life [15,16], low satisfaction with medical care [17] and decreased treatment adherence [18]. About 80% of patients experience elevated distress about one months after completion of primary treatment [19]. Fortunately, distress is transient for the majority of patients with cancer (±67%), for whom distress levels remain low or which decline swiftly after treatment completion [20-22]. Fifteen to 21% report stable high levels of distress up to 15 months post-diagnosis which may not remit spontaneously

[20,21,23]. Additional support and/or a referral to health care services may alleviate the problems distressed patients suffer from.

Screening for distress and referral wish in clinical practice

Since the last quarter of the past century, attention to psychosocial problems of patients with cancer in clinical practice gradually increased and the subspecialty of psycho-oncology emerged [24]. Distress has been recognized as the '6th vital sign' after blood pressure, temperature, respiration, pulse, and pain [12]. Clinical practice guidelines on routine screening for distress have been developed in several countries such as the United States [13], United Kingdom [25], Canada [26], Australia [27] and the Netherlands [28]. These guidelines are an important step towards improving access to psychosocial and supportive health care.

The first version of the Dutch guideline 'Screening for psychosocial distress' (in Dutch: '*Detecteren behoefte psychsociale zorg'*) was published in 2010 and a revised version came out in 2017 [28]. The Dutch guideline describes several steps in the distress management process: 1) Distress screening by completion of a distress screening questionnaire; 2) discussion of patients' response patterns on the distress screening questionnaire, and; 3) referral to appropriate services, if needed or wished, for treatment of identified problems [28].

The Distress Thermometer (DT) showed to be a helpful tool in distress screening of patients with cancer [13,29-31]. This tool combined with the Problem List (PL), is central in the distress management guideline of the United States [13], Canada [26] and its validated Dutch version in the Dutch guideline [28]. The Dutch DT/PL (in Dutch: *'Lastmeter';* see appendix A for the Dutch and English versions of the DT/PL) assesses distress (scale ranging from 0-10), underlying problems covering the practical, social, emotional, spiritual and physical domains and includes a question concerning patients' referral wish to a psychosocial or supportive health care professional [32]. Based on the international literature [30], the Dutch guideline (version 2017), perceives a patient as clinically distressed if patients report a DT score of 4 or higher (DT cutoff score; [28]). During the last few years, routine screening with the Dutch DT/PL has been implemented in many oncology clinics in the Netherlands.

Guidelines for distress screening are widely disseminated but debate exists about whether distress screening should be implemented in clinical practise as the evidence on the effectiveness of distress screening seems inconsistent. However, recent reviews of the literature showed that distress screening has modest but significant benefits, especially on secondary outcomes such as communication with health care professionals

and referral to additional supportive health care services [28,33]. Noteworthy, distress screening is a vital component of the distress management process but is not valuable in itself [28]. Without appropriate management of distress and underlying problems, systematic adoption of distress screening in clinical practice is probably not worthwhile [33]. Thus, screening should be followed by an intervention and/or referral of (distressed) patients to enhance its effectiveness.

Although the DT/PL has been recommended as the preferred tool for screening and monitoring distress [34], knowledge about associates of high distress, underlying problems and referral wish as measured by the DT/PL is limited. Instruments for distress screening in psycho-oncology often measure different areas of distress and thus, findings from studies concerning other distress screening questionnaires cannot be compared [35]. First, DT/PL validation studies mainly used mixed samples of patients with cancer. However, patients with cancer should not be perceived as a homogeneous group [36,37]: distress levels, DT cutoff scores and underlying problems may vary across different cancer subpopulations. For example, it is unclear whether distress levels, DT cutoff scores, underlying problems (PL) vary by cancer type [30]. Identical responses on the DT/PL across cancer types may not reflect the same in terms of clinically elevated scores. This information is valuable in the discussion of patients' response patterns on the DT/PL and may guide subsequent actions to be taken by health care professionals. Additionally, knowledge about factors related to high distress may further assist in the identification of patients at risk of developing clinically elevated distress and can further guide clinical decision making of whom to refer to additional supportive health care services.

Second, few studies examined DT/PL responses in cancer survivors who are beyond the first year after completion of primary treatment i.e. longer-term cancer patients/survivors [38]. As longer-term patients with cancer may experience lower emotional functioning and may suffer from lingering problems, even years after diagnosis [39,40], these studies may provide important knowledge about the severity of distress, nature of problems, and referral wish in this population. Several studies examined the course of distress over time in breast cancer survivors who were within the first 15 months after diagnosis [23,41]. A study using the DT/PL showed that one in five patients with breast cancer reported clinically elevated distress at both 6 and 15 months postdiagnosis [23]. However, no studies are known assessing DT/PL responses over time in longer-term (breast) cancer survivors. These studies may give important insight into the development and course over time and what factors are associated with continuing elevated distress.

Third, the literature on factors associated with patients' referral wish to psychosocial and supportive health care services is sparse and results are mostly contradictory. Knowledge of predictors may aid in the identification of patients who are in need of a referral [42]. This is especially important since distress and referral wish, though positively related, are not completely congruent. Not all distressed patients express a referral wish and some patients with low distress desire a referral (e.g. [32]).

In sum, better insight into the prevalence and factors associated with experiencing (continuing) high distress, underlying problems and into the factors related to having a referral wish as measured with the DT/PL can aid in timely identification and adequate management of patients' distress and problems.

Web-based interventions to support patients with cancer

Timely management of prevailing problems is important to appropriately assist patients with cancer in adjusting to the cancer experience. Many patients wish for information about symptoms/problems that may arise after treatment completion and about strategies how to cope with these problems [43,44]. The internet has been recognized as a viable medium by which patients can be educated and supported regarding distress caused by psychosocial and physical problems [45]. Web-based support programs can be of important value in management of these symptoms for several reasons. First, considering the growing number of patients with cancer, the health care system is urged to develop cost-effective interventions that are less resource intensive. Second, a shift from more traditional physician/caregiver care models towards patient centered-care models is emerging and calls for a higher involvement and increased self-management by patients. Educating patients regarding self-management of existing symptoms usually occurs during short encounters at the oncology clinic. However, patients need information and support throughout the entire illness trajectory [46,47]. Web-based support programs can satisfy these needs. Other advantages of web-based support programs are its wide availability, accessibility, and ability to provide patient-tailored information and support [48-53].

Although new web-based support programs emerge at a rapid pace [54], relatively little is known about their effects on cancer patient reported outcomes. In patients with chronic diseases, these programs have been linked to positive outcomes such as increases in knowledge, perceived social support, and in empowerment and improved health behaviors [55,56]. The available review studies in patients with cancer demonstrated promising but mixed efficacy [57,58]. The included studies in these reviews were often of poor quality in terms of study design and/or content of the web-based support programs

(i.e. non-professionally led).

Psychosocial distress is common among cancer patients, especially during the first year after primary treatment completion (i.e. re-entry phase [59]) as patients may struggle with psychosocial as well as physical difficulties. Tailored information and support are of marked importance during this phase to prevent and/or treat lingering problems. To date, only few rigorously tested web-based interventions for patients with cancer in the re-entry phase are available [60,61].

In sum, web-based programs which educate and support patients with cancer seem to have great potential but more evidence is needed to establish the value of these programs in supporting patients with cancer.

Study aims

As patients with cancer frequently experience distress from psychosocial and physical symptoms, adequate detection of these symptoms and referral wishes are essential to ensure that patients receive the psychosocial and/or supportive health care they need [62,63]. Detection requires appropriate identification of patients in need. The first part of this thesis aims to increase insight into the prevalence and associates of (continuing) high distress, underlying problems and referral wish as measured by the Dutch DT/PL.

Chapter 2 examines differences in DT cutoff scores, distress levels, and underlying problems between patients with different cancer types and stages. DT cutoff scores are helpful in deciding which patients may suffer from clinically elevated distress. The effect of socio-demographic and illness-related variables on distress are also examined. Knowledge of the relationship between these variables and the level of distress may further aid in the identification of patients at risk for clinically elevated distress. A large heterogeneous sample of patients with cancer is included (N=1340) varying in socio-demographic and illness-related characteristics including cancer type and stages and varying in distress levels. **Chapter 3** uses the same large sample and focuses on patients' referral wish. The main study objective is to examine the effects of patients' perceived distress and underlying problems, socio-demographic and illness-related variables, and social support sufficiency on referral wish. We are especially interested in the variables that uniquely affect referral wish. **Chapter 4** focuses specifically on DT/PL responses of longer-term survivors of breast cancer i.e. survivors who finished treatment with adjuvant chemotherapy 1-5 years earlier. The study aims to contribute to our understanding of (clinically elevated) distress levels, problems, referral wish and health care use in this population over a one-year time period. Also, variables associated with continuing elevated distress (i.e. a DT score of ≥5 at both measurements points) are explored.

The second part of this thesis examines the effects of web-based support programs on patient reported outcomes. As the available literature on the effect of these programs is limited, more information is needed to decide whether these programs can be used to support patients in clinical practice.

Chapter 5 reviews the current literature on the effects of web-based support programs on psychosocial and physical symptoms of patients with cancer. Only studies that were (randomized) controlled trials including a comparison group and web-based programs that were developed or moderated by (a) health care professional(s) are included. The methodological quality of the included studies is evaluated and discussed. **Chapter 6** describes a multicenter randomized controlled trial which examines the effects of a web-based tailored psycho-educational program for patients with breast cancer in the re-entry phase (ENCOURAGE program). The program aims to empower patients to take control over prevailing problems and to adjust to life after treatment. A problem-solving orientation is adopted in the development of the psycho-educational material as well as use of approach-oriented coping strategies. Several self-reported outcomes are assessed including patients' optimism and feelings of control over the future. Finally, **Chapter 7** provides an overall discussion of the findings as presented in the preceding chapters as well as suggestions for clinical practice and future research.

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PART 1

DISTRESS, PROBLEMS AND REFERRAL WISH IN CANCER PATIENTS

CHAPTER 2

Do cancer and treatment type affect distress?

J.M. Admiraal[1], A.K.L. Reyners[1], J.E.H.M. Hoekstra-Weebers[2,3]

[1]Department of Medical Oncology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands
[2]Comprehensive Cancer Center Netherlands, Groningen, the Netherlands
[3]Wenckebach Institute, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands

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ABSTRACT

Objective: We examined differences in distress levels and Distress Thermometer (DT) cutoff scores between different cancer types. The effect of socio-demographic and illness-related variables on distress was also examined.

Methods: 1350 patients (response=51%) completed questions on socio-demographic and illness-related variables, the Dutch version of the DT and Problem List, and the Hospital Anxiety and Depression Scale. Receiver operating characteristics analyses were performed to determine cancer specific cutoff scores. Univariate and multivariate effects of socio-demographic and illness-related variables (including cancer type) on distress were examined.

Results: Prostate cancer patients reported significantly lower DT scores (M=2.5$\pm$2.5) and the cutoff score was lower (≥4) than in patients with most other cancer types (M varied between 3.5-5.0; cutoff=≥5). Multivariate analyses (F=10.86, p<.001, R^2=0.08) showed an independent significant effect of four variables on distress: intensive treatment (β=0.10, any (combination of) treatment but surgery only and 'wait and see' (W&S)); a non-prostate cancer type (β=-0.17); the interaction between gender and age (β=-0.12, highest distress in younger women as compared to older women and younger and older men); and the interaction between cancer type and treatment intensity (β=0.08, lowest scores in prostate cancer patients receiving non-intensive treatment as compared to their counterparts).

Conclusions: Distress and cutoff score in prostate cancer patients were lower than in patients with other cancer types. Additionally, younger women and patients receiving treatment other than surgery only or W&S are at risk for higher distress. These results can help identify patients possibly in need of referral to professional psychosocial and/or allied health care.

INTRODUCTION

Patients confronted with a diagnosis of cancer face numerous stressors in the physical, emotional, social, practical and/or spiritual life domains [1,2]. Between 25 and 50% of cancer patients experience clinically elevated psychosocial distress for which professional care may be needed [3,4]. Distress has been recognized as the sixth vital sign after blood pressure, temperature, respiration, pulse, and pain, suggesting that distress screening should be part of conventional cancer care [5].

Appropriate screening and early identification of problems are essential to ensure that patients receive the psychosocial and/or allied professional health care they need [6-8]. During the last years, the need for psychosocial screening has been recognized and guidelines on systematic screening and distress management have been formulated by several professional organizations [9]. The Distress Thermometer (DT), originally developed in 1998 [10], showed to be a valuable tool in psychosocial screening of cancer patients [10-12]. The DT combined with the Problem List (PL) consisting of items covering the practical, social, emotional, spiritual and physical domains is central in the distress management guideline of the National Comprehensive Cancer Network [11], and its validated Dutch version in the Dutch guideline [13,14]. During the last few years, routine screening with the Dutch DT/PL has been implemented in many oncology clinics in the Netherlands.

Since its development, the DT/PL have been validated in many countries worldwide. The optimal DT cutoff score for identifying clinically distressed patients reported in the 27 studies found in the literature varied from no cutoff point found [15]), to ≥3 [16,17], ≥4 [18-30], ≥5 [10,13,31-36], ≥6 [37] and ≥7 [38,39]. The Hospital Anxiety and Depression Scale (HADS) was used in 67% of the studies to determine optimal DT cutoff scores [13,16-22,24,25,28,29,31,34-38].

A reason for the differences in cutoff scores found in the literature may be type of cancer, besides possible cultural and methodological reasons [16]. It has been argued that much has to be learned about the instrument's validity when applied in specific cancer populations [40]. Cancer patients should not be perceived as a homogeneous group concerning the psychosocial and physical difficulties they may experience [4,41]. Validation has mainly been performed in patient samples with varying cancer types. A consistent overrepresentation of breast cancer patients (≥30%) is present in the majority of these validation studies, including the Dutch [13,17,19,20,22,26,29,31,32,38 ,39]. The high number of breast cancer patients may have exerted a significant effect on distress levels and cutoff estimates. Until now, it remains unclear whether distress

levels and DT cutoff scores depend on cancer type. Additionally, because of the more limited rule-in ability of the DT [3], knowledge of which patient' socio-demographic and illness-related characteristics are associated with higher DT scores may support adequate identification of patients at risk for clinically elevated distress [4].

To our knowledge, no study has made a systematic attempt to identify optimal cut-off scores, signaling clinically elevated distress, for different cancer types. The aim of the present study was two-fold: 1) to examine the hypothesis that distress levels and cutoff scores depend on cancer type and/or treatment; 2) to examine the effect of socio-demographic and illness-related variables on patients' perceived distress.

METHODS

Patients

This study was conducted in the surgical, medical, gynecologic and urologic oncology departments of twenty-two hospitals in the Netherlands. Patients who were aware of their cancer diagnosis and treatment plan were approached for study participation. Eligible patients were in a 'wait and see' (W&S) condition (prostate cancer patients only), under active treatment, or visited the hospital for follow-up after treatment completion. Patients had to be aged ≥18 years, physically and cognitively able to complete the questionnaire, and sufficiently fluent in Dutch.

Procedures

Study coordination was performed by the Comprehensive Cancer Center Netherlands, location Groningen (CCCN). All twenty-three hospitals in the North-Eastern CCCN region were approached and 19 agreed upon study participation. Three hospitals situated elsewhere in the Netherlands requested to participate. The study was performed according to the regulations of the medical ethical committee of the University Medical Centre Groningen and followed the ethical guidelines of the participating hospitals. Depending on the number of patients yearly diagnosed with cancer in a hospital (information gained from the Netherlands Cancer Registry, CCCN) between 30-300 questionnaires were handed out. All patients visiting the outpatient clinics meeting the inclusion criteria were invited by their physician or nurse for study participation. Patients willing to participate received written information about the study aims, procedures, contact information of the investigators, the questionnaire, an informed consent form, and a prepaid return envelope. Patients were recruited until all questionnaires were handed out which usually took between 2 to 4 weeks.

Measures

The following socio-demographic and illness-related characteristics were assessed through the self-report questionnaire: age, gender, marital status, children, education completed (range: primary (1) – university (6)), employment status (full-time job; part-time job; self-employed; sickness/invalidity benefit; unemployed; unable to work; retired; student; voluntary work), cancer type, date of diagnosis, treatment modalities and treatment phase (W&S, under active treatment, or in follow-up). Patients were placed in a curative or palliative treatment intent group by a medical oncologist on the basis of cancer type and treatment.

Distress was measured using the Dutch DT/PL [11,13]. The DT consists of a single item that asks patients to indicate the amount of overall distress experienced during the past week on a 11-point scale. Scores range from 0-10 (no to extreme distress). The Dutch PL incorporates 47 items. Patients can indicate whether or not (yes/no) they experienced practical (7 items), family/social (3 items), emotional (10 items), religious/spiritual (2 items) and physical problems (25 items). Patients were asked to rate from 1-10 the amount of distress they experienced for each item in the problem list they answered 'yes'. The last question of the questionnaire covered patients' referral wish (yes, maybe or no) to a psychosocial (psychologist, psychiatrist, social or pastoral worker) or allied (physical therapist, dietician) health care professional [13].

The Hospital Anxiety and Depression scale (HADS) is a 14-item self-report questionnaire that assesses symptom severity of anxiety and depression [42]. The HADS has been used in many different populations, including cancer patients [42,43]. Its validity and reliability have been well-established. The questionnaire consists of two 7-item subscales: an anxiety and a depression subscale. Scores range from 0-21 for each subscale with higher scores indicating higher levels of anxiety/depression. A score of ≥15 has been indicated to be the ideal cutoff score representing clinically significant emotional distress [42].

Data analysis

Descriptive analyses were calculated for the socio-demographic and illness-related variables, the DT/PL and the HADS. PL subscale scores were computed by taking the mean of the total scores of the items within each subscale. If a patient had a missing value on a variable relevant for a specific analysis, he/she was not included in that analysis.

Receiver operating characteristics (ROC) analyses [44] were used to examine what DT score most adequately distinguished between HADS cases and non-cases. The HADS score of ≥15 implying caseness was used as the gold standard. Cutoff scores were established on the optimal tradeoff between sensitivity and specificity values (sensitivity≥specifity). Separate ROC curves were computed for the different cancer types. Positive likelihood ratio's (LR+), positive predictive values (PPV) and negative predictive values (NPV) were calculated for each cancer type's optimal DT cutoff score. Cancer type was categorized into breast (including 7 men), prostate, digestive, lung, gynecologic, head/neck, sarcoma/bone, hematologic, skin or urologic (other than prostate) cancer. The last group consisted of patients with other types of cancer (17 liver, 6 brain, 2 thyroid and 2 multiple cancers). Statistical power software (PASS [45] showed a required sample of $N \geq 45$ to obtain an AUC of 0.80 with 80% power (DT≥5=20% [13], two-sided tests).

Independent-samples t-test, one-way independent ANOVA's, and Pearson's correlations were conducted to explore univariate effects on the DT. ANOVA's were computed to examine the effect of cancer type on PL subscale scores. Small-sized effects[46] could be detected with 80% power for (two-sided) t-tests, correlations and ANOVA's (d≥0.18-d≥0.24 *(N*2/*N*1=2-6), ρ=0.10 and f=0.09-f=0.12 (3-11 subgroups) respectively) with *N*=1100 (G*power [47]). Hochberg's GT2 post-hoc tests were executed to correct for differences in sample sizes across cancer types, treatment types and phases. Welch F was reported in case of violation of the homogeneity of variance assumption. Socio-demographic and illness-related variables showing an univariate significant effect on the DT were entered into a hierarchical multiple regression analysis (first step). Previous research showed high distress levels in young and female patients [41,48] and low distress in prostate cancer patients [4,48,49] in the W&S [50]. Therefore, interaction terms for age (centered scores)×gender and treatment intensity×cancer type were entered into the second step to examine the additional value over and above the main effects. Simple slope analyses were performed to interpret significant interaction effects. To estimate slopes for patients low and high in age values of –1SD and +1SD from the mean were used, respectively [51,52]. Power analyses (G*power [47]) showed 80% power to detect a small-sized effect (f^2=0.02 [46]) with inclusion of 24 variables *(N*=1150).

RESULTS

Patient characteristics

A total of 2640 eligible patients were invited to participate in the study, of whom 1352 returned the questionnaire (response=51%). Two patients were excluded because they were aged <18 years. Ten questionnaires were excluded due to data incompleteness. Table 1 displays patients' characteristics, DT descriptives and the univariate effects on the DT.

Table 1. *Patient characteristics, DT scores and univariate effects on DT scores (N varied between 1165-1340 in analyses).*

Characteristics		DT	Univariate test	
		Mean ± SD	Test statistic	*p*
Age (mean ± SD(range))	61.0 ± 11.6 (21.2-89.0)		*r*=-0.2	*p*<.001
Gender (*N*(%))			*t*=-3.8	*p*<.001
Men	501 (37.4)	3.4 ± 2.6		
Women	839 (62.6)	4.0 ± 2.6		
Marital status (*N*(%))			*t*=0.7	ns
Married/cohabiting	1117 (83.4)	3.7 ± 2.6		
Single/widowed/divorced	223 (16.6)	3.9 ± 2.7		
Children (*N*(%))			*t*=0.7	ns
Yes	1126 (84.0)	3.7 ± 2.6		
No	214 (16.0)	3.9 ± 2.8		
Children living at home (*N*(%))			*t*=-2.6	*p*<.01
Yes	328 (24.8)	4.1 ± 2.6		
No	995 (75.2)	3.6 ± 2.7		
Educational level (mean ± SD(range))	3.9 ± 1.8 (1-8)		*r*=0.0	ns
Daily activities (*N*(%))			*t*=-1.0	ns
Employed	432 (33.1)	3.9 ± 2.6		
Not employed	875 (66.9)	3.7 ± 2.7		
Time since diagnosis (mean ± SD(range))	2.0 ± 3.0 (0.0-33.8)		*r*=0.0	ns
Treatment intent (*N*(%))			*t*=-1.1	ns
Curative	1124 (85.7)	3.7 ± 2.6		
Palliative	187 (14.3)	3.9 ± 2.7		
Treatment phase (*N*(%))			*F*=14.1	*p*<.001
Wait&see	21 (1.6)	1.8 ± 2.5		
Under active treatment	589 (44.3)	4.1 ± 2.5		
Follow-up	721 (54.2)	3.5 ± 2.7		
Treatment type (*N*(%))			*F*=8.9	*p*<.001
Surgery	274 (20.9)	3.0 ± 2.6		
Surgery+radiotherapy	213 (16.2)	3.6 ± 2.8		
Surgery+chemotherapy	239 (18.2)	4.3 ± 2.5		
Surgery+radiotherapy+chemotherapy	262 (20.0)	4.4 ± 2.3		
Surgery+immunotherapy and/or hormonal therapy	22 (1.7)	2.8 ± 2.8		
Radiotherapy	78 (5.9)	2.6 ± 2.3		
Chemotherapy	119 (9.1)	3.9 ± 2.5		
Chemotherapy+radiotherapy	56 (4.3)	4.3 ± 2.5		
Immunotherapy/hormonal therapy	28 (2.1)	4.0 ± 3.3		
Wait&see	21 (1.6)	1.8 ± 2.5		

Preliminary results

Patients' mean DT score was 3.8 (*SD*=2.7); 41% scored ≥5. Most problems were experienced in the emotional and physical domains. Fatigue (58%), physical fitness/condition (54%), tension/nervousness (41%), emotional control (37%), and sleep (36%) were reported most frequently on the PL.

Univariate effect of cancer type on DT/PL

Cancer type had a significant effect on DT score, $F(10,1186)=5.0$, $p<.001$. Consequent Hochberg's GT2 post-hoc tests showed that prostate cancer patients experienced significantly less distress than patients with breast, digestive, lung, gynecologic, head/neck and 'other' cancers (Table 2).

Significant univariate effects were found of cancer type on the practical, emotional, social and physical domains (Table 2). Hochberg's GT2 analysis revealed that prostate cancer patients experienced less distress in the practical domain than breast, gynecologic and sarcoma/bone cancer patients; in the emotional domain than breast and gynecologic cancer patients; and in the physical domain than breast, lung, digestive and 'other' cancers. Lung cancer patients reported significantly lower distress in the practical and social domains than breast cancer patients. Patients with 'other' cancers experienced more physical problems than head/neck and sarcoma/bone patients.

Cutoff scores

The ROC curve of breast cancer patients showed an area under the curve (AUC) of 0.82 (95%CI 0.77-0.86). A cutoff score of 5 on the DT showed optimal diagnostic accuracy with correct classification of 85% of HADS cases (sensitivity) and 66% of HADS non-cases (specificity). The corresponding LR+ was 2.48: breast cancer patients scoring ≥5 on the DT were 2.5 times more likely to be a HADS case than a HADS non-case. ROC curves of digestive, gynecologic and head/neck patients (AUC ranged between 0.72-0.84) also showed a cutoff score of 5. ROC analyses of prostate (AUC 0.77; 95%CI 0.62-0.92), sarcoma/bone (AUC 0.87; 95%CI 0.76-0.97) and lung cancer patients (AUC 0.80; 95%CI 0.67-0.92) showed an optimal tradeoff between sensitivity and specificity at a score of 4 (Table 3). However, analysis of the male lung cancer patients (*N*=55/78, 71%) showed an AUC of 0.80 (95%CI 0.66-0.95), sensitivity 75%, specificity 63%, resulting in a cutoff score of 5. No ROC analyses were performed for hematologic, skin, urologic and 'other' cancers.

Table 2. *DT and PL descriptives, HADS cases for each cancer type and comparison between groups (N varied between 1090-1274 in ANOVA's).*

	Breast	Prostate	Digestive	Lung	Gyneco-logic	Head/ Neck	Sarcoma/ bone	Hemato-logic	Skin	Urologic	Other	Univariate test	
												Test statistic	*p*
N (%)	575 (43.3)	171 (12.9)	147 (11.1)	98 (7.4)	88 (6.6)	85 (6.4)	50 (3.8)	39 (2.9)	27 (2.0)	22 (1.7)	27 (2.0)#		
DT													
N scoring ≥5/DT respondents (%)	215/504 (42.7)	40/151 (26.5)	61/134 (45.5)	39/85 (45.9)	32/81 (39.5)	34/83 (41.0)	20/49 (40.8)	14/37 (37.8)	10/26 (38.5)	11/22 (50.0)	15/25 (60.0)		
Mean ± SD (R=0-10)	3.9 ± 2.6***	2.5 ± 2.5	4.1 ± 2.6***	4.1 ± 2.5***	3.8 ± 2.9*	3.7 ± 2.8*	3.7 ± 2.7	3.4 ± 2.6	3.5 ± 2.7	4.3 ± 2.3	5.1 ± 2.4***	*F*=5.0	*p*<.001
PL subscales (Mean ± SD)													
Practical (R=0-70)	5.2 ± 7.6***	1.1 ± 3.2	3.4 ± 7.1	2.2 ± 6.1†	4.4 ± 8.1*	2.9 ± 5.5	6.2 ± 9.4***	2.3 ± 6.4	5.0 ± 6.9	4.8 ± 7.5	4.4 ± 11.5	*F*=11.6	*p*<.001
Social (R=0-30)	1.7 ± 4.1	0.9 ± 3.1	1.0 ± 3.5	0.3 ± 1.3†	1.9 ± 4.0	1.1 ± 2.3	1.7 ± 4.5	0.5 ± 1.7	1.7 ± 3.9	2.4 ± 4.8	1.3 ± 4.4	*F*=5.6	*p*<.001
Emotional (R=0-100)	14.2 ± 17.1***	7.0 ± 12.1	12.2 ± 16.0	8.7 ± 12.8	16.5 ± 19.1***	12.2 ± 14.8	13.8 ± 16.4	9.2 ± 16.4	11.8 ± 17.1	12.2 ± 13.8	13.8 ± 17.6	*F*=4.1	*p*<.001
Spiritual (R=0-20)	1.4 ± 3.4	0.8 ± 2.9	1.1 ± 2.8	1.0 ± 3.4	1.0 ± 3.0	1.3 ± 3.0	2.4 ± 4.6	1.0 ± 3.4	0.7 ± 2.2	0.7 ± 2.2	1.1 ± 2.5	*F*=1.2	ns
Physical (R=0-250)	28.6 ± 29.1**	17.8 ± 21.4	33.0 ± 29.9***	32.9 ± 28.4*	25.5 ± 27.6	24.2 ± 23.0‡	22.4 ± 22.0‡	29.4 ± 29.6	20.7 ± 26.2	31.3 ± 24.8	45.4 ± 36.1***	*F*=4.6	*p*<.001
HADS													
N scoring ≥15/HADS respondents (%)	88/551 (16.0)	16/165 (9.7)	39/142 (27.5)	19/88 (21.6)	13/80 (16.3)	15/74 (20.3)	10/50 (20.0)	6/37 (16.2)	3/24 (12.5)	3/21 (14.3)	8/27 (29.6)		

#11 missing

R=possible range

*Different from prostate cancer at *p*<.05;**p*<.01;***p*<.001; †different from breast cancer at *p*<.05; ‡different from 'other' cancers at *p*<.05

Table 3. *Results of receiver operating characteristics analyses for cancer types.*

	N completing DT+HADS	**Cutoff point**	**Sensitivity**	**Specificity**	**LR+**	**PPV**	**NPV**
Breast	488	5	0.85	0.66	2.48	0.32	0.96
Prostate	147	4	0.86	0.76	3.56	0.28	0.98
Digestive	131	5	0.71	0.65	2.00	0.43	0.86
Lung	78	4	0.87	0.52	1.82	0.33	0.94
Gynecologic	73	5	0.92	0.69	2.94	0.37	0.98
Head/neck	72	5	0.77	0.63	2.06	0.35	0.91
Sarcoma/bone	49	4	1.00	0.65	2.86	0.42	1.00

Univariate effect of patient characteristics

Age, gender, children living at home, treatment phase, and treatment type significantly univariately affected the DT score (Table 1). Patients who were younger, female or had children living at home experienced higher distress levels than their counterparts. As for treatment phase, post-hoc test revealed significant differences between all phases: patients in the W&S condition had lowest scores and patients under active treatment had highest scores. Concerning treatment type, post-hoc tests showed that patients receiving surgery only, radiotherapy only and patients in the W&S condition reported experiencing lower distress than patients undergoing surgery and chemotherapy; surgery, radiotherapy and chemotherapy; or chemotherapy and radiotherapy. Patients receiving chemotherapy *only* reported significantly higher distress than patients undergoing radiotherapy only and patients in the W&S condition.

Further inspection revealed that the 45 prostate cancer patients undergoing radiotherapy only reported significantly lower distress (M=1.9$\pm$2.0) than the 25 non-prostate cancer patients undergoing radiotherapy only (M=4.0$\pm$2.1; t=4.0, p<.001). The mean distress score of this last patient group was similar to that of non-prostate cancer patients receiving other treatment types (p=1.0).

Multivariate model predicting DT score

The variable cancer type was dichotomized into prostate versus non-prostate cancer type. Treatment type was dichotomized into non-intensive (surgery only + prostate cancer patients in the W&S condition and those receiving radiotherapy only (66% of prostate cancer patients)) versus intensive treatment (all other treatment types + the remaining 34% prostate cancer patients) based on the results of previous analyses.

Multiple hierarchical regression analysis showed that 8% of the variance was explained by the variables included in the model (F=10.86, p<.001). Of the variables included in the first step, intensive treatment and having a non-prostate cancer type appeared to have a significant unique effect. The interaction terms of age×gender and treatment intensity×cancer type, entered in the second step, each had a significant independent effect on the DT score (Table 4).

Table 4. *Hierarchical multiple regression analysis, final model (N=1151).*

	β	***R²***	***R²Ch***	***FCh***
Step 1		0.07		12.68***
Age	-0.03			
Gender	-0.00			
Children living at home	-0.03			
Prostate cancer(y/n)	-0.17***			
Treatment intensity	-0.10**			
Under active treatment†	-0.05			
Wait&see†	-0.00			
Step 2		0.08	0.01	4.25*
Interaction age×gender	-0.12*			
Interaction treatment intensity×prostate cancer(y/n)	-0.08*			

*p< .05;**p<.01;***p<.001
†dummy

Simple slope analyses revealed a significant effect of age on distress in women (β=-.17, p<.001) but not in men (β=-.03, p=.57). Women's mean distress level decreased from younger (DT_{mean}=4.3) to older age (DT_{mean}=3.4) whereas mean distress in men was comparable across ages (DT_{mean}=3.5 younger age; DT_{mean}=3.4 older age). Younger women's distress was higher than that of younger men (β=.15, p<.01) but no gender difference was found at older age (β=.01, p=.84). Simple slopes of treatment intensity×prostate cancer showed significantly lower distress (β=-.17, p<.001) in non-intensively treated prostate cancer patients (DT_{mean}=1.9) than in non-intensively treated non-prostate cancer patients (DT_{mean}=3.2). The difference (β=-.05, p=.27) between intensively treated prostate cancer patients (DT_{mean}=3.7) and intensively treated non-prostate cancer patients (DT_{mean}=4.1) was not significant. Non-intensively treated cancer patients reported lower distress than intensively treated patients, both in prostate cancer patients (β=1.8, p<.001) and in non-prostate cancer patients (β=.86, p<.001).

DISCUSSION

The current study aimed first to examine differences in distress levels and cutoff scores between patients diagnosed with different cancers. Prostate cancer patients reported experiencing less distress than patients with breast, digestive, lung, gynecologic, head/neck and liver/brain/thyroid cancers. Also, a lower cutoff of ≥4 on the DT was found for prostate cancer patients than the cutoff of ≥5 for breast, digestive, gynecologic and head/neck cancer patients. Lower distress in prostate cancer patients compared to patients with other types of cancer has been reported previously [4,48,49,53]. Lower distress in prostate cancer patients seems to be partly treatment-related while not gender-related (see fifth paragraph in the discussion). Two thirds of the prostate cancer patients in the present study were in watchful waiting, or underwent surgery or radiotherapy only. These non-intensively treated prostate cancer patients reported lower distress than intensively treated prostate cancer patients and than intensively *and* non-intensively treated non-prostate cancer patients. In support of our findings, earlier studies reported lower distress in prostate cancer patients in watchful waiting [50] and lower quality of life in prostate cancer patients receiving hormonal treatment [54,55]. In sum, and in support of our first hypothesis, distress levels and cutoff scores seem to depend both on cancer and treatment type.

An explanation for the lower distress found in prostate cancer patients is that many prostate cancer patients receive the information that the disease will probably not be the cause of death [56]. Hence, patients may perceive their condition as chronic rather than as life-threatening. A further explanation might be that prostate cancer patients, particularly those treated non-intensively, experience less physical impairment due to illness-and treatment-related factors than patients with other cancer types [53]. This is supported by the present study's finding that prostate cancer patients reported less problems in the physical, practical, and emotional domains than patients with other cancer types.

An optimal DT score of ≥4 was also obtained for lung and sarcoma/bone cancer patients. However, the limited ability (specificity 52%) to identify non-clinically distressed lung cancer patients when using a cutoff score of ≥4 should be noted. Analyses of male lung cancer patients showed a cutoff of ≥5 yielding a higher specificity value (63%). Similarly, the sensitivity value of sarcoma/bone cancer patients was suspiciously high (100%), possibly caused by the small number of patients included. Hence, it should be examined whether a cutoff score of ≥4 holds in studies that include larger samples of lung and sarcoma/bone cancer patients.

The Dutch distress management guideline [14] stresses the importance of discussing the DT/PL response pattern and appropriate referral of patients scoring above the DT's cutoff. We would recommend to always discuss the response pattern with a patient, using the cutoff score (either ≥4 or ≥5 depending on cancer type and treatment intensity) as a first screen. A DT score below the cutoff does not exclude that a patient may suffer greatly from a specific problem for which referral may be necessary.

The second aim was to study the effect of socio-demographic and illness-related variables on distress. In addition to the effects of cancer type and treatment intensity, multivariate analyses showed higher distress levels in younger women as compared to younger men, older men and older women. Other studies [4,48,57] including one using the DT [58], found that age or gender were associated with higher distress. The present study shows that it is the combination of gender and age that matters. It has been suggested that younger women respond differently to cancer than older women possibly due to personal and familial challenges that accompany an earlier life stage [59]. Many young women are highly involved in child-rearing and/or a professional career. Additionally, disfigurement of the body, sudden menopause, decreases in libido and vaginal dryness may be of great impact on young women's (sexual) relationships [48,59].

Only eight percent of the variance in patients' distress levels was explained by the variables included in the model suggesting that cancer, treatment type and age/gender have limited effect on patient reported distress levels. Other variables such as personality, perceived control and social support [60-62] may play a greater role. The effect of such characteristics should be examined in addition to the risk variables identified in the present study.

The DT has been identified as a valid and effective tool in ruling out clinically-elevated distress [12,58]. The rule-in ability is more limited and consequently, it has been recommended not to use the DT alone [3,12]. As such, the higher distress levels in non-prostate cancer patients, patients receiving more intensive treatment and younger women found in the present study may assist in the identification of patients at risk of developing clinically elevated distress and can further guide clinical decision making of whom to refer to professional psychosocial and/or allied health care.

Distress screening, as performed in the present study, is a vital component of distress management though not valuable in itself [58]. A future challenge is to conduct studies examining the effectiveness of distress management programs following screening [1,38,63] with special need for randomized controlled trials [58]. Distress screening and management programs should both be effective and efficient. Considering the growing number of cancer patients, computer-based programs seem a promis-

ing venue for future distress screening and management [48,64].

The current study had some limitations. ROC analyses for some cancer types could not be performed or were of lower quality due to small sample sizes. Secondly, the HADS and the DT are not fully congruent [13]. The HADS questionnaire measures anxiety and depression whereas the DT more broadly assesses distress covering practical, social, emotional, spiritual and physical complaints. The finding that more patients scored above the DT cutoff than above the HADS cutoff reflects the DT's multidimensional nature. Thirdly, the response rate was 51% which may affect generalizability. No information was available from non-respondents because patients were approached for participation by their health care provider in the hospital and anonymous to the researchers. However, a large population of cancer patients was included varying in socio-demographic and illness-related characteristics and in distress, thus making comparisons possible.

Other clear advantages can be noted. The current study was the first to examine cutoff scores for separate cancer types. ROC analyses displayed clear cutoff scores and satisfying sensitivity and specificity estimates for a number of cancer types, underlining the value of our findings. Finally, we could identify patient' risk factors for high distress which can be important in the process of clinical decisions making.

In summary, the distress level and cutoff score in prostate cancer patients appear to be lower than in patients with other cancer types. Particularly prostate cancer patients who underwent surgery or radiotherapy only or who were in the W&S condition reported low distress. Patients receiving treatment other than surgery only and younger women are at risk for higher distress. Screening for distress and knowledge of risk factors may facilitate identification of clinically distressed patients possibly in need of additional psychosocial and/or allied professional health care.

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CHAPTER 3

Cancer patients' referral wish: effects of distress, problems, socio-demographic and illness-related variables, and social support sufficiency

J.M. Admiraal[1a], F.M. van Nuenen[1b,2], J.G.M. Burgerhof[1c], A.K.L. Reyners[1a], J.E.H.M. Hoekstra-Weebers[1b,2]

[1]University of Groningen, University Medical Center Groningen, Groningen, the Netherlands
[a]Department of Medical Oncology
[b]Wenckebach Institute
[c]Department of Epidemiology
[2]Netherlands Comprehensive Cancer Organisation

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ABSTRACT

Background: The present study's aim was to examine effects of cancer patients' perceived distress and problems, socio-demographic and illness-related variables, and social support sufficiency on referral wish.

Methods: A cross-sectional group of 1340 patients (response=51%) completed a questionnaire consisting of: the Dutch version of the Distress Thermometer and Problem List (PL), including the referral wish question; and questions on socio-demographic and illness-related variables and perceived social support sufficiency. Univariate and multivariate analyses were performed to investigate the effects of these variables on patients' referral wish.

Results: Of the patients who completed the referral wish question (n=1297), 13% wished and 21% considered a referral, while 66% did not want a referral. Univariate analyses showed that, in comparison to patients not having a referral wish, those having a (maybe) wish were more distressed, reporting more problems in all PL domains, younger, more likely not to have children or children living at home, higher educated, more likely to be employed, under active treatment or recently diagnosed, receiving more intensive treatment, and more likely to perceive support received to be insufficient. A final ordinal logistic regression analysis showed independent effects of distress, practical and emotional problems, age, and treatment phase on referral wish ($\chi^2(6)=205.9$; $p<0.001$; Nagelkerke's $R^2=0.24$).

Conclusions: A third of the patients (maybe) wished a referral. Knowledge of risk variables (particularly increased distress, experience of more practical and emotional problems, younger age, and receiving active treatment or recently diagnosed) may support the identification of patients at increased need of additional health care services.

INTRODUCTION

Distress is frequently encountered by cancer patients during treatment and follow-up. Between 30% and 40% of cancer patients experience *clinically* elevated psychosocial distress for which professional care may be needed [1,2]. Elevated distress levels have been associated with reduced health-related quality of life [3,4], low satisfaction with medical care [5], and decreased treatment adherence [6]. Therefore, guidelines were developed by professional organizations [7,8] to ensure that distress management would be an integral component of oncology practice.

According to the Dutch guideline "Detection of Need for Care", appropriate distress management entails several steps: 1) completion of the Dutch version of the Distress Thermometer (DT) and Problem List (PL) to detect distress level, problems or unmet needs underlying the distress, and a patient's referral wish to professional health care services; 2) discussion of patients' response patterns on the DT/PL, and; 3) referral to appropriate services, if needed or wished, for treatment of identified problems [9].

A number of studies provide insight into factors associated with distress or unmet needs (e.g. [10-12]). However, the literature on factors associated with patients' referral wish to psychosocial and paramedical health care services is relatively sparse and results are mostly contradictory. It is important to identify predictors of referral wish since knowledge of predictors may aid in the identification of patients who are willing to accept a referral [13].

Several studies showed that distress is significantly related to referral wish [12-17] but other studies found no such relationship [18,19]. Younger age has been associated consistently with an increased likelihood that patients desire a referral [15-17,19,20]. However, no consistent relationship with referral wish was found of other socio-demographic variables such as educational level and relationship status [15-17,19,20]. Also, the literature is inconclusive as to the effect of illness-related variables, such as type of treatment received [15,19]. The heterogeneity in study outcomes (desire for psychological support [17,19], need for services [15], need for help [13], actual referral [20], or access of services [16]) and measurement instruments used may account for the different findings. Additionally, some studies specifically focused on a single treatment (patients receiving chemotherapy [13]), time period (newly diagnosed [16]), or patient group (breast cancer [17], metastatic lung or gastro-intestinal cancer [20]) limiting the generalizability of the findings. All in all, no conclusive evidence is available on the effects of distress or socio-demographic and illness-related factors on referral wish.

Patients who perceive their social environment as supportive report a higher quality of life, better psychological health, less supportive health care needs or are less often referred [20-23]. Therefore, we hypothesize that patients who experience sufficient social support are less likely to have a referral wish for additional psychosocial and/or paramedical health care than patients who perceive the social support they receive as insufficient.

The present study aims to contribute to our understanding of which patients would be more likely to wish a referral. To our knowledge, this is the first study including a large heterogeneous sample of cancer patients and a diverse set of variables to examine its effects on referral wish. This will enable us to draw more firm conclusions. The objectives of the current study were: (1) to examine associations between cancer patients' referral wish, patients' distress and underlying problems; (2) to investigate associations between referral wish and socio-demographic and illness-related variables and perceived social support sufficiency; and (3) to study unique effects of variables significantly affecting referral wish.

METHODS

Patients and procedures

Patients aware of their cancer diagnosis and treatment plan, aged ≥18 years, physically and cognitively able to complete the questionnaire, and sufficiently fluent in Dutch, were approached for study participation irrespective of time since diagnosis, intent, phase and type of treatment. All 23 hospitals in the North-Eastern region of the Netherlands were approached. Nineteen agreed upon study participation. Three hospitals situated elsewhere in the Netherlands requested to participate. Staff from surgical, medical, gynecologic and/or urologic outpatient oncology clinics recruited patients, consecutively visiting these clinics, for the study. Consenters were given the questionnaire to complete at home and return anonymously to the Netherlands Comprehensive Cancer Organisation (IKNL), who coordinated the study. Consequently, questionnaire responses were not discussed with patients. The study was performed according to the regulations of the medical ethical committee of the University Medical Centre Groningen and followed the ethical guidelines of the participating hospitals. Study procedures and patients have been described in detail elsewhere [10].

Measures

Socio-demographic (age, gender, relationship status, children, highest education level completed (range from 1=primary school only to 7=university), employment status, and illness-related characteristics (cancer type, date of diagnosis, treatment type, treatment phase) were assessed through self-report questions. A medical oncologist placed patients in a curative or palliative treatment intent group on the basis of cancer type and treatment.

Perceived social support sufficiency was assessed by a single item. Patients were asked whether they perceived the support they had received from their family and broader social environment had been sufficient (yes/no).

The self-report Dutch DT/PL was used to assess distress, problems experienced and referral wish [8,14]. The DT is a single item asking patients to indicate the amount of distress experienced during the past week on a 11-point scale, ranging from 0-10 (no to extreme distress). The DT cutoff score for identifying clinically distressed patients was ≥5 [14]. On the Dutch PL, patients can indicate whether or not (yes/no) they experienced practical (7 items), family/social (3 items), emotional (10 items), religious/spiritual (2 items) and physical problems (25 items). Patients were asked to rate from 1-10 the amount of distress they experienced for each item in the problem list they

answered 'yes'. The last question of the Dutch DT/PL covers patients' referral wish to a psychosocial or paramedical health care professional [14]. Answer categories were: 'yes', 'maybe' or 'no' (Appendix 1[1]).

Analysis

Descriptive analyses were calculated for socio-demographic and illness-related variables, social support sufficiency, and the DT/PL. Relationship status was dichotomized into 'relationship' (married and cohabiting patients) and 'no relationship' (single, widowed, divorced and LAT (=living-apart-together)) [24]. Treatment type was dichotomized into non-intensive (surgery only and patients in the 'watchful waiting' condition) versus intensive treatment (any other type or combination of treatment) [10,14]. The 'watchful waiting' treatment phase group was merged with the 'follow-up' group and the 'recently diagnosed' with the 'under active treatment' group in further analyses to avoid expected values <5 and because responses on the referral wish question in the combined groups were comparable. PL domain scores were computed by adding the scores of the items within each domain.

Chi-square tests, one-way ANOVA's and Kruskal-Wallis tests were performed to explore univariate effects of the variables on referral wish. When a chi-square was significant, post-hoc pairwise comparisons of column proportions with Bonferroni adjusted p-values were used to examine significant differences between referral wish groups. Significant Kruskal-Wallis tests were followed by Mann-Whitney U-tests with post-hoc Bonferroni corrections.

Variables showing a univariate significant effect on referral wish were entered into two separate multivariate ordinal regression analyses to examine independent effects on referral wish: the first including the DT and PL subscales, and the second including the socio-demographic and illness-related variables and social support sufficiency. Variables with the highest p-value were removed in a stepwise fashion until all included variables added significantly to the model ($p \leq 0.05$). Significant variables from these two analyses were entered into a final model (forced entry method). The negative log-log link function was used to calculate the effect of the variables on referral wish since lower categories (no vs. maybe and maybe vs. yes) were more probable [25]. The coefficients (exp(-B)) of this link function represent the ratio of two log transformed cumulative probabilities. A positive B indicates a higher probability of referral wish for higher values of the explanatory variable. Statistical model assumptions were checked for violations (e.g. adequacy of

1 Appendix 1 can be found in Appendix A in this thesis

expected frequencies, absence of multicollinearity and proportional odds). Nagelkerke R^2 was used as a measure of goodness of fit for the entire model [26].

RESULTS

Patients

As reported earlier [10], the response rate was 51%. Data of 1340 patients were analyzed. Table 1 depicts patients' characteristics and the univariate effects of these variables on referral wish. Of the respondents to the referral wish question (N=1297), 13% wished (*N*=167), 21% considered (*N*=272), and 66% (*N*=858) did not want a referral to a psychosocial or paramedical health care professional.

Table 1. Patients' characteristics and univariate effects on patients' referral wish (N varied between 1195 and 1297 in analyses)

	Referral wish			
Characteristics	**No**	**Maybe**	**Yes**	**Test statistic**
Referral wish (*N*(%))	858 (66)	272 (21)	167 (13)	
Age (mean ± SD)	62.2 ± 11.2[a]	58.8 ± 11.5[b]	57.4 ± 12.3[b]	F=18.2***
Gender (*N*(%))				χ^2=4.0
Men	335 (69)	88 (18)	62 (13)	
Women	523 (64)	184 (23)	105 (13)	
Relationship status (*N*(%))				χ^2=4.3
Relationship	714 (67)	215 (20)	131 (13)	
No relationship	141 (60)	57 (24)	36 (15)	
Children (*N*(%))				χ^2=9.8**
Yes	740 (68)	213 (20)	140 (13)	
No	118 (58)	59 (29)	27 (13)	
Children living at home (*N*(%))				χ^2=23.3**
Yes	195 (61)	70 (22)	56 (17)	
No	540 (71)	142 (19)	82 (11)	
No children	112 (57)	58 (29)	27 (14)	
Educational level (median(IQR))	4.0 (2.0-5.0)[a]	4.0 (3.0-6.0)[b]	4.0 (3.0-5.0)[ab]	H=7.6*
Employment status (*N*(%))				χ^2=7.9*
Employed	254 (61)	102 (24)	63 (15)	
Not employed	580 (69)	165 (20)	101 (12)	

Table 1. (Continued)

	Referral wish			
Characteristics	**No**	**Maybe**	**Yes**	**Test statistic**
Cancer type (*N(%)*)				χ^2=11.0
Breast	349 (63)	124 (22)	81 (15)	
Prostate	112 (69)	30 (19)	5 (12)	
Digestive	97 (69)	30 (21)	15 (11)	
Lung	61 (64)	20 (21)	14 (15)	
Gynecologic	59 (69)	22 (26)	5 (6)	
Head/Neck	60 (71)	15 (18)	10 (12)	
Sarcoma/Bone	33 (68)	10 (20)	6 (12)	
Other^	81 (71)	19 (17)	14 (12)	
Time since diagnosis (years) Median(IQR)	1.0 (0.4-2.2)	0.9 (0.4-1.8)	1.0 (0.5-2.2)	*H*=1.0
Treatment intent (*N(%)*)				χ^2=0.6
Curative	718 (66)	227 (21)	143 (13)	
Palliative	122 (67)	39 (22)	20 (11)	
Treatment phase (*N(%)*)				χ^2=12.8**
Watchful waiting/Follow-up	494 (70)	134 (19)	75 (11)	
Recently diagnosed/Receiving treatment	358 (61)	137 (23)	91 (16)	
Treatment intensity (*N(%)*)				χ^2=15.5***
Non-intensive	241 (73)	64 (19)	26 (8)	
Intensive	598 (64)	201 (22)	137(15)	
Social support sufficiency (*N(%)*)				χ^2=38.9***
No	40 (39)	35 (34)	28 (27)	
Yes	806 (68)	235 (20)	138 (12)	

Percentages may vary between 99-101% due to rounding
F=ANOVA; X^2=Chi-square; *H*=Kruskal-Wallis
*p<0.05; **p<0.01; ***p<0.001
Groups with different superscripts differ significantly from each other
IQR=Interquartile range
^Other=hematologic(39), skin(27), urologic(22), liver(17), brain(5), thyroid(2), unknown(2)

Univariate effect of distress and problems on referral wish

Median DT scores differed significantly between all three referral wish groups: patients indicating a referral wish had the highest median DT score and patients having no referral wish had the lowest. Also, referral wish and scoring under/above the DT cutoff were associated (Table 2). Pairwise comparisons showed that the proportion of patients with a DT score above the cutoff who (maybe) wished a referral was significantly higher than the proportion of patients who scored under the cutoff.

Mann-Whitney post-hoc tests showed differences between all three referral wish groups in the practical domain of the PL. In the remaining domains, differences were

found between patients who wished or considered a referral and patients not wishing a referral (Table 2).

Table 2. Descriptives of DT/PL and univariate effects of DT/PL on referral wish (N varied between 1081 and 1267 in analyses)

	Referral wish			
	No	**Maybe**	**Yes**	**Test statistic**
DT				
Median(IQR) (r=0-10)	3 (1-5)[a]	5 (3-7)[b]	6 (3-7)[c]	H=147.0***
N scoring ≥5(%)	245 (50)	144 (29)	103 (21)	χ^2=97.7***
N scoring <5(%)	540 (77)	111 (16)	52 (7)	
PL subscales (Median(IQR))				
Practical (r=0-58)	0 (0-3)[a]	3 (0-8)[b]	6 (0-14)[c]	H=125.7***
Social (r=0-30)	0 (0-0)[a]	0 (0-3)[b]	0 (0-5)[b]	H=103.3***
Emotional (r=0-84)	3 (0-11)[a]	14 (6-31)[b]	21 (9-38)[b]	H=198.2***
Spiritual (r=0-18)	0 (0-0)[a]	0 (0-3)[b]	0 (0-3)[b]	H=72.7***
Physical (r=0-175)	2 (2-32)[a]	32 (15-58)[b]	38 (24-57)[b]	H=149.6***

X^2=Chi-square; H=Kruskal-Wallis; ***p<0.001
IQR=Interquartile range
r=observed range
Groups with different superscripts differ significantly from each other

Univariate effect of patient characteristics on referral wish

Eight variables were significantly associated with referral wish (Table 1). Patients who were younger or had higher education were more likely to consider or wish a referral than their counterparts. Patients who had no children or were employed were significantly more likely to consider a referral and less likely to have no referral wish than patients with children or who were not employed. A higher proportion of patients who had children living *at home* expressed a referral wish than patients who had no children living at home.

Regarding treatment phase, a higher proportion of patients who were in follow-up or watchful waiting did not want a referral while a higher proportion of patients who were under active treatment or recently diagnosed did express a referral wish. Patients who received intensive treatment were significantly more likely to express a referral wish and less likely to express no wish than patients who received non-intensive treatment.

Lastly, significantly more patients who experienced insufficient social support (may-

be) wished a referral and fewer had no referral wish than patients who experienced sufficient support.

Multivariate analysis

The test of parallel lines evaluating the proportional odds assumption was satisfied for the ordinal regression analyses, reflecting the appropriateness of the negative log-log ordinal models. No serious violations of the adequacy of expected frequencies were observed.

The first regression analysis, including the DT and all PL subscales, showed independent significant effects of three variables: patients reporting a higher score on the DT, and on the practical and emotional domains were more likely to consider or wish a referral ($\chi^2(3)=201.3$, $p<.001$; Nagelkerke's $R^2=0.23$) (Table 3). Of the eight variables included in the second regression analysis, three showed a unique significant effect on referral wish (Table 3). Patients who were younger, who were under active treatment or recently diagnosed, and those who experienced insufficient social support were more likely to consider or wish a referral ($\chi^2(3)=76.2$; $p<0.001$; Nagelkerke's $R^2=0.07$). The final model ($\chi^2(6)=205.9$; $p<0.001$; Nagelkerke's $R^2=0.24$) showed independent significant effects of distress, practical and emotional problems, age, and treatment phase (Table 4).

Table 3. Separate ordinal regression analyses including: 1) the DT/PL (N=977) and; 2) socio-demographics, illness-related characteristics and social support sufficiency univariately associated with referral wish^ (N=1228)

Variables	Estimate	Standard Error
DT	0.114***	0.028
PL subscales		
Practical	0.022**	0.007
Emotional	0.024***	0.004
Age	-0.022***	0.004
Treatment phase		
Follow-up/watchful waiting[a]		
Recently diagnosed/under active treatment	0.357***	0.097
Social support sufficiency		
No[a]		
Yes	-0.899***	0.141

^variables with an independent significant effect are depicted

**$p<0.01$; ***$p<0.001$

[a]=Reference category

Table 4. Final ordinal regression analysis (N=957)

Variables	Estimate	Standard Error
DT	0.101***	0.029
PL subscales		
Practical	0.020**	0.007
Emotional	0.022***	0.004
Age	-0.015**	0.005
Treatment phase		
Follow-up/watchful waiting[a]		
Recently diagnosed/under active treatment	0.263*	0.115
Social support sufficiency		
No[a]		
Yes	-0.263	0.183

*p<0.05; **p<0.01; ***p<0.001

[a]=Reference category

DISCUSSION

The current study, including a large heterogeneous sample of cancer patients, examined effects of perceived distress and problems, socio-demographic and illness-related variables, and social support sufficiency on referral wish. Independent significant effects of five variables were found, namely patients who experienced more distress, more problems in the practical and/or emotional domain, who were under active treatment or recently diagnosed, and/or those who were younger were more likely to express a referral wish. Nine additional variables were univariately related: patients experiencing more problems in the social, spiritual and physical domains were more likely to have a (maybe) referral wish, as were patients who had no children or children living at home, who had completed a higher educational level, were unemployed, received intensive treatment, and who indicated that the social support they had received was insufficient.

The finding that distress level was associated with referral wish has been observed previously [13,27,28], also in smaller heterogeneous Dutch samples [12,14,15]. The likelihood that a patient with a high distress score (DT≥5) expressed a referral wish appeared to be three times as high as that in a patient with a low score. Distress level and emotional and practical problems appeared to be more powerful predictors of referral wish than socio-demographic or illness-related variables and social support sufficiency. This has not been reported before and suggests that a DT/PL response pattern provides more information when deciding on whom to refer than socio-demographic or illness-related variables and support sufficiency. However, distress was not decisive. Half of the high distressed patients reported no referral wish, while a small but substantial percentage with low distress did express a referral wish. Similar findings were reported in previous studies [14,15]. These results suggest that screening for distress is helpful in identifying patients with high symptom burden but insufficient to determine who would desire or need additional care, even when used in combination with the risk variables identified in the present study. This underlines the importance of discussing DT/PL responses and referral wish with all patients, regardless of their distress level, as recommended in the Dutch guideline [9].

Discussing responses may reveal why patients who experience *high* distress report *no* referral wish. A common reason for not desiring a referral is a preference to rely on informal social support such as family and friends [29,30]. This was also supported by our findings that support sufficiency was related to a decreased referral wish. Secondly, patients may not be aware of available services. A recent review study showed that

19% of cancer patients lacked information regarding availability of various health care services [31]. Therefore, patients should be well informed about the various sources of additional care that they could be referred to for the specific psychosocial, physical, spiritual and practical concerns they experience. Thirdly, patients may question whether the (intensity of) distress they experience is normal. Normalizing feelings and pointing out problems usually experienced by fellow cancer patients may decrease distress. Finally, patients may not wish a referral because of concerns about stigma. About 10% of patients reported stigma as a reason for not wanting psychosocial care [31]. De-stigmatizing psychosocial care may encourage patients with unmet needs to accept such care. Communication between a clinical staff member and a patient may uncover reasons such as mentioned above, possibly leading to referral and uptake of professional care. Similarly, discussion with patients reporting an overall low level of distress may reveal why and for which specific problem a patient requires a referral. Asking patients directly about the need for services, as has been suggested as a substitute for screening for distress, would provide insufficient information. We argue for a process that includes collecting information from patients about distress, problems and need for referral *and* discussing responses with patients to adequately decide whether one should refer and to whom.

Distress associated with underlying problems in all PL domains was related to referral wish. The only other study that, to the authors' knowledge, examined relationships between the PL and referral wish multivariately found that emotional problems were associated with desiring help in lung cancer patients [27]. In contrast, we found that practical problems also had a unique effect. An explanation may be that lung cancer patients reported having fewer practical problems than patients diagnosed with other cancers [10]. Studies not using the PL showed that referral (wish) was related to emotional [13,19,20], marital [19], physical [19], and spiritual [20] difficulties, which support our results.

Additionally, several socio-demographic and illness related variables were associated with referral wish. Similar to earlier research, we found that younger patients were more likely to wish a referral [15,19,20,32]. In confirmation of our hypothesis, we found that the experience of insufficient social support was among the most important predictors of referral wish in the model including socio-demographic and illness-related variables. Patients may receive social support from different sources [33,34]. Our study shows that having adult children (those *not* living at home) was associated with a lower likelihood of desiring a referral suggesting that adult children may be a significant source of social support. Conversely, parents who had children living at home (age being a potential confounder) were more likely to wish a referral. Patients who face cancer treatment while having dependent children at home are often confronted with multiple problems possi-

bly causing distress [35]. For example, parents may feel unable to protect their children from being forced to deal with their parent's cancer. Also, maintaining household routines is often difficult and may require that children or others help with tasks traditionally performed by the parent [36]. Future research is required to establish the exact role of different social support sources and perceived sufficiency with regard to referral wish. Particularly because when including the DT and the practical and emotional problem domains, the contribution of social support sufficiency on referral wish became non-significant. It may well be that distress as measured with the DT encompasses distress associated with perceived social support insufficiency from sources such as mentioned above.

Of the illness-related variables included in the current study, treatment phase affected referral wish most strongly. Our results show that health care professionals should pay particular attention to the psychosocial or paramedical health care needs of patients *during* cancer treatment, while it has often been suggested that attention should be particularly focused on the first year after treatment completion [37].

Considering the multivariate model, the pseudo R^2 was relatively low indicating that model fit can be improved by inclusion of other, possibly more relevant, variables. For example, future research may examine the effect of previous (negative) encounters with health care services and patients' perceived benefit. These variables have been suggested as significant barriers in the delivery and uptake of health care services [16,30]. Identification of additional variables may further increase insight into determinants of patients' referral wish.

Some limitations of the current study should be noted. The design of the study was cross-sectional. Consequently, we should be careful with conclusions regarding causality. Secondly, social support sufficiency was assessed with a single item. Questionnaires that measure perceived social support using multiple items and answer categories may provide a finer-grained picture of patients' perceived social support sufficiency. However, the finding that perceived social support sufficiency differed between all three referral wish groups reflects the adequacy of our social support measure. Thirdly, the response rate (51%) was relatively low. No information was available from non-respondents because patients were approached for participation by their health care provider in the hospital and thus, anonymous to the researchers. Finally, women (62.6%) were overrepresented as were breast cancer patients (43.3%) considering 10-year prevalence in the Netherlands (53% and 22%, respectively [38]). This may have biased the results. However, neither gender nor cancer type were found to affect referral wish.

The current study had several strengths. The study used a large heterogeneous sample of cancer patients which enabled us to investigate possible effects of a large number

of variables on referral wish. Important differences were detected between the referral wish groups on a number of variables which may help health care providers to identify patients with a possible desire for additional health care.

The current study provides valuable information for clinical practise. To adequately manage cancer patients' distress, we recommend health care professionals to be particularly attentive to patients who report high distress and underlying emotional and practical problems, to younger patients, and to patients who currently receive treatment, because these patients seem to have an increased desire for a referral. Future research may focus on the effects and cost-effectiveness of a distress screening process, consisting of screening, discussion of responses and appropriate referral on patient reported outcomes.

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CHAPTER 4

Distress, problems, referral wish and supportive health care use in breast cancer survivors beyond the first year after chemotherapy completion

J.M. Admiraal[1], J.E.H.M. Hoekstra-Weebers[2], C.P. Schröder[1]
W. Tuinier[1], G.A.P. Hospers[1], A.K.L. Reyners[1]

[1]University of Groningen, University Medical Center Groningen, Department of Medical Oncology, Groningen, the Netherlands
[2]University of Groningen, University Medical Center Groningen, Wenckebach Institute, Groningen, the Netherlands

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ABSTRACT

Purpose: We examined distress levels, problems, referral wish and supportive health care use in a cross-sectional group of breast cancer survivors at two-time points with a one-year time interval. Also, factors related to continuing elevated distress were explored.

Methods: Breast cancer survivors, 1-5 years after chemotherapy completion, filled in the Dutch Distress Thermometer/Problem List (DT/PL) and questions on background characteristics at study inclusion (T1). DT/PL responses and health care use were discussed during semi-structured interviews. One year later, re-assessment took place (T2). The data were analyzed by descriptive and univariate analyses. Continuing elevated distress was defined as a DT score ≥5 at T1 and T2.

Results: Seventy-three survivors completed all questionnaires (response=84.6%). Eighteen (25%) experienced continuing elevated distress. Fatigue (T1 N=48 (66%); T2 N=41 (56%)) and lack of physical fitness (T1 N=44 (60%); T2 N=36 (49%)) were most often reported. Time since diagnosis, health care use, and practical, social, emotional and physical problems were significantly associated with continuing elevated distress. Between diagnosis and T1, 42 (67%) used supportive healthcare services, mostly a psychologist and/or a physical/lymphedema therapist, and between T1-T2, 39 (53%) did. At T1, 8 (11%) expressed a referral wish and at T2, 11 (16%) did.

Conclusions: Screening and management of distress, problems and referral wish are important, even years after chemotherapy completion as a substantial proportion of breast cancer survivors continue to report elevated distress and problems. Special attention should be paid to survivors reporting physical problems, especially fatigue and lack of physical fitness, since these problems are most strongly related to continuing elevated distress.

INTRODUCTION

Breast cancer is the most prevalent cancer in women worldwide [1]. Due to earlier diagnosis and advances in treatment, the five-year survival rate of breast cancer increased from 74 to 88% between 1981 and 2015 in the Netherlands [2]. With the growing number of breast cancer survivors, understanding of not only physical but also psychosocial functioning beyond diagnosis and treatment is essential for optimal survivorship care for this population.

Receiving a diagnosis of cancer and undergoing treatment poses challenges to survivors' coping abilities. Survivors can experience tumor- or treatment-related physical difficulties such as fatigue, insomnia, and sexuality-related problems, and these problems may persist into longer-term survivorship [3-6]. Additionally, they may face emotional, social, spiritual and/or practical problems [7-9].

The problems patients experience altogether are often referred to as 'distress' [10]. According to the transactional model of stress and coping of Lazarus and Folkman (1984), distress arises when an individual appraises that the demands of the stressor (e.g. cancer) exceed personal resources (the survivor's ability to cope with cancer) [11]. Distress has been associated with reduced health-related quality of life [12,13], low satisfaction with medical care [14], and decreased treatment adherence [15]. Distress seems transient for most cancer survivors, but 15-21% of the survivors report stable high levels of distress up to 15 months post-diagnosis [16,17]. Consequently, it has been recommended to routinely screen for distress in cancer survivors to detect problems for which referral may be indicated. The National Comprehensive Cancer Network (NCCN, US) guideline for distress management was the first to recommend to screen all cancer patients with the Distress Thermometer (DT), a questionnaire specifically developed for cancer patients [10]. The NCCN also advises to use a Problem List (PL) that investigates which problem(s) in the practical, social, emotional, spiritual and/or physical domain underlie the reported level of distress. The DT in combination with the PL has a good reliability and internal consistency [18]. A meta-analysis including 42 studies from 20 countries, including 14,808 cancer patients varying in cancer and treatment type, showed that the DT is a highly useful and valid screening tool to detect distress [19].

The Dutch guideline on screening and monitoring distress describes a process that encompasses: 1) completion of the Dutch version of the DT/PL, including a question on referral wish; 2) discussion of the completed DT/PL with patients, and (3) referral to appropriate healthcare services if needed or wished [20]. Following the stress-coping model of Lazarus and Folkman, survivors should be approached on how to optimize

their ability to cope and reduce their burden. The Dutch guideline describes a process that is in line with this stress-coping approach. Adequate referral to supportive health care services after exploring survivors' referral wish can aid in enhancing effective coping strategies and reducing the burden of the problems experienced [20]. Also, a screening process coupled with discussion and referral according to pre-determined pathways showed to be more effective with respect to doctor-patient communication and number of referrals than a screening process without these components [21-23].

Although the DT/PL has been recommended as the preferred tool for screening [24], little is known about DT/PL responses of breast cancer survivors who are beyond the first year after completion of primary treatment i.e. longer-term cancer survivors. Samples often include a mixture of survivors who are within the first year after primary treatment (re-entry phase [6]), long-term survivors (5+ years after diagnosis [25]) and survivors who are in between (longer-term survivors). This makes it difficult to gain insight into the severity of distress, nature of problems, and referral wish of longer-term survivors [26-28]. Additionally, several studies examined the course of distress over time in breast cancer survivors who were within the first 15 months after diagnosis [17,29]. However, no studies are known assessing DT/PL responses over time in longer-term (breast) cancer survivors. As longer-term breast cancer survivors may suffer from lingering emotional and physical problems (e.g. [3]), longitudinal studies may provide important information about the prevalence of distress and the underlying problems over time. Also, knowledge about supportive health care use and referral wish can further increase insight into their needs.

The present study aims to contribute to our understanding of (clinically elevated) distress levels, problems, referral wish and health care use in longer-term breast cancer survivors over a one-year time period. Moreover, we explored which socio-demographic and illness-related variables and underlying problems were associated with continuing elevated distress.

METHODS

Patients

Survivors were recruited from the outpatient clinic of the Department of Medical Oncology of the University Medical Center Groningen (UMCG). Female breast cancer survivors who consecutively visited their medical oncologist for a routine follow-up visit and who had completed adjuvant chemotherapy 1-5 years earlier were invited to participate (longer-term survivors). Eligibility criteria were: age ≥18 years, stage I-III breast cancer, no recurrent cancer, physically and cognitively able to complete a questionnaire and be interviewed, and sufficiently fluent in Dutch. The study was approved by the medical ethical committee of the UMCG.

Procedures

Eligible survivors received a letter at home with information about study aims and procedures, the questionnaire, an informed consent form and contact information of the investigators, one week before the routine follow-up visit. Survivors deciding to participate were requested to return the completed informed consent form and questionnaire in a prepaid return envelope to the UMCG before the visit (T1). Informed consent was obtained from all individual survivors included in the study. Immediately after the routine follow-up visit, enrolled survivors received a semi-structured interview (±20 min) with a specially trained oncology nurse or research psychologist in which responses on the DT/PL were discussed, brief psycho-education was provided (in case of problems), the need for a referral to additional supportive care services was explored and supportive health care use since diagnosis was assessed (first cross-sectional assessment; T1). Single sessions (e.g. intake) with a health care professional were not considered as care. Survivors expressing a referral wish were referred to a relevant health care professional or were instructed how to access the health care service that was requested.

The DT/PL was sent to participating survivors 1 year later together with an invitation for a second interview (second cross-sectional assessment; T2). Survivors who forgot to return the DT/PL or who were not scheduled for a follow-up visit (to a medical, surgical or radiation oncologist) 1 year later were offered an interview by telephone. Up to three attempts by phone were made to contact survivors who did not return the DT/PL.

Measures

Self-report questions assessed the following socio-demographic characteristics at T1: age, marital status, presence of children, educational level (range: primary (1)-univer-

sity (6)), and employment status (employed for wages; not-employed). Illness-related characteristics (date of diagnosis, pTNM-classification, cancer stage (I-III, derived from pTNM-classification), medical treatment, and date of completion of last chemotherapy cycle were collected from the survivors' medical records.

Distress, problems and referral wish were measured using the Dutch DT/PL [8,10], at T1 and T2. The DT consists of a single item that asks cancer survivors to indicate the amount of overall distress experienced during the past week on an 11-point scale (0-10; no to extreme distress). The Dutch DT/PL has been validated for cancer patients with different diagnoses and treatments [8,9]. A DT cutoff score of ≥5 represents clinically elevated distress in Dutch breast cancer survivors. The sensitivity was 0.85, specificity 0.66, positive predictive value 0.32 and negative predictive value 0.96 [9]. On the 47-item PL, cancer survivors can indicate whether or not (yes/no) they experienced practical, family/social, emotional, religious/spiritual, and physical problems. Survivors were asked to rate from 1-10 the amount of distress they experienced for each item in the PL they answered 'yes'. Internal consistency and reliability of the PL is good (Cronbach's alpha=0.90). Lastly, the questionnaire assesses cancer survivors' referral wish (yes, maybe or no) to a health care professional (psychologist, social or pastoral worker, oncology nurse, physical therapist or dietician), peer support from a fellow patient, and/or to other types of health care [8].

During the interview at T1 and T2, patients were asked whether they had received care from a psychologist, social or pastoral worker, sexologist, physical therapist, lymphedema therapist, dietician and/or whether they were enrolled in a rehabilitation program combining physical and cognitive-behavioral therapy. Uptake of other types of health care was also explored.

Data analysis

The percentage of missing values ranged from 0 to 11.7%. Missing data patterns were examined with Little's missing completely at random test with a chi-square statistic ($p<.05$), and descriptive analyses, i.e., separate-variance t-tests, cross tabulations, and a tabulated pattern table. The results showed that the data could be assumed to be missing at random, i.e. missingness was predicted by variables that were part of the dataset. Five imputations were generated for the missing data by use of the fully conditional specification algorithm (non-monotonous data) [30,31]. The variables referral wish and referral by the research team were not imputed because of the small N for these variables and many possible outcomes: imputations were perceived as unreliable.

Descriptive statistics were calculated for socio-demographic and illness-related characteristics, the DT/PL, and health care use. Continuing elevated distress was defined as a DT score of ≥5 at both T1 and T2. Continuing low distress was assumed when patients reported a DT score of <5 at both timepoints. Survivors who developed recurrent/metastasized breast cancer or another malignancy during the study period were excluded at T2.

Associations between DT/PL scores and changes herein over time (ΔT1 – T2) and time since diagnosis and time since chemotherapy were calculated by Spearman's correlations to explore the effect of time on DT/PL responses. Chi-square tests and Mann-Whitney U tests were performed to explore univariate effects of socio-demographic and illness-related characteristics, health care use (dichotomized (Yes/No), problem domains and problem items at T1 on continuing elevated distress (patients with a DT score of ≥5 at both T1 and T2 versus patients with a DT score of ≤4 at one or both time points). Effect sizes (ES) were reported for significant results to examine the clinical relevance (Cramers's V (V) for chi-square tests; r for Mann-Whitney U tests). An ES of 0.1 indicates a small effect, 0.3 a medium effect and 0.5 a large effect [32, 33]. Statistical analyses were performed using SPSS, version 24 (SPSS Inc. Chicago, IL).

RESULTS

Patient characteristics

Seventy-seven of the 91 eligible survivors approached during the 1.5 year of the study at the UMCG, agreed to participate in the study (response=84.6%; Figure 1). The main reasons for survivors to decline study participation were a lack of interest to talk about their current psychosocial health status (N=7) or they did not feel comfortable discussing psychosocial issues (N=3). Chemotherapy completion varied between 1.0-4.8 years at study entry, and patients were on average three years after diagnosis (range=1.6-5.2). Fifty-four (74%) patients were receiving hormonal treatment at T1; 44 at T2 (60%, Table 1).

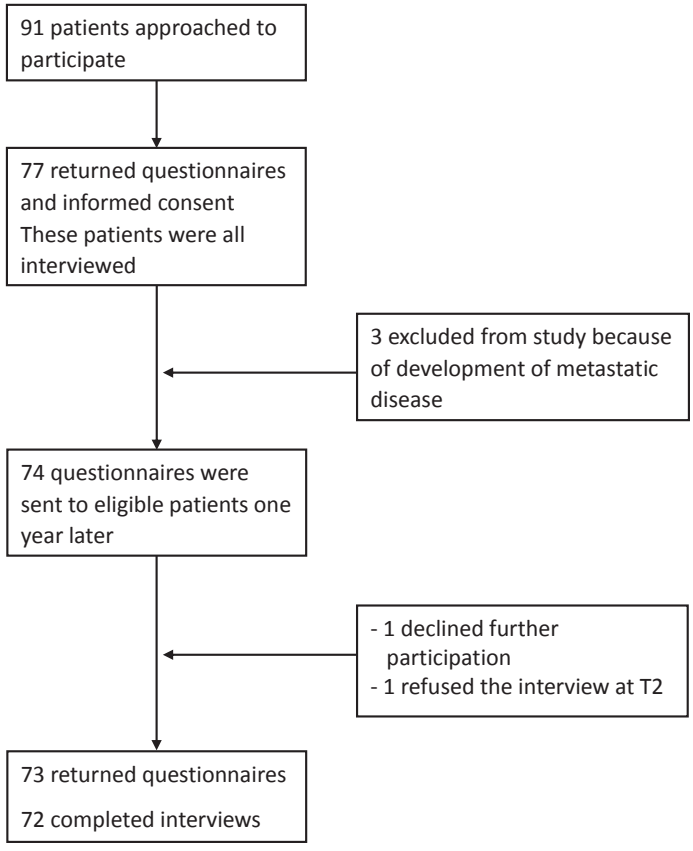

Figure 1. Flow chart of the study

Table 1. Patient characteristics at T1 and univariate associations with continuing elevated distress (*N*=73).

Characteristic	Median (IQR)	*N* (%)	*Test statistic[ab] (p)*
Age (years)	52.1 (45.7-56.6)		*U*=437.8 (.440)
Marital status			χ^2=0.0 (.967)
Single/widowed/divorced		12 (16.4)	
Married/living together		61 (83.6)	
Children			χ^2=1.1 (.292)
No		21 (28.8)	
Yes		52 (71.2)	
Educational level	4.0 (3.0-5.0)		*U*=491.5 (.928)
Employment			χ^2=3.8 (.054)
Not employed		30 (41.1)	
Employed		43 (58.9)	
Stage of cancer			χ^2=1.4 (.495)
I		11 (15.1)	
II		49 (67.1)	
III		13 (17.8)	
Time since diagnosis (years)	2.8 (2.1-3.7)		*U*=336.2 (.040)
Time since chemotherapy completion (years)	2.2 (1.6-3.4)		*U*=397.0 (.198)
Surgery			χ^2=0.7 (.406)
Lumpectomy		31 (42.5)	
Mastectomy		42 (57.5)	
Systemic adjuvant therapy			χ^2=6.5 (.091)
Chemotherapy			
Chemotherapy and immunotherapy		12 (16.4)	
Chemotherapy and hormonal therapy		7 (9.6)	
Chemotherapy, immunotherapy and		45 (61.6)	
hormonal therapy		9 (12.3)	
Hormonal therapy at T1			χ^2=0.0 (.871)
No/completed		19 (26.0)	
Yes		54 (74.0)	
Hormonal therapy at T2			χ^2=0.0 (.899)
No/completed[a]		29 (39.7)	
Yes		44 (60.3)	
Adjuvant radiotherapy			χ^2=0.5 (.488)
No		31 (42.5)	
Yes		42 (57.5)	
Breast reconstruction			χ^2=0.4 (.509)
between diagnosis and T1			
No		57 (78.1)	
Yes		16 (21.9)	

Table 1. (Continued)

Characteristic	*Median (IQR)*	*N (%)*	*Test statistic[ab] (p)*
between T1 and T2			χ^2=0.1 (.726)
No		59 (80.8)	
Yes		14 (19.2)	
Health care use			χ^2=8.2 (.004)
between diagnosis and T1			
No		24 (32.9)	
Yes		49 (67.1)	
between T1 and T2			χ^2=5.5 (.022)
No		34 (46.6)	
Yes		39 (53.4)	

[a] = Average test result across imputed datasets

[b] = Continuing elevated distress was defined as a DT score of ≥5 at *both* T1 and T2.

U=Mann-Whitney U test; X2=Chi-square; IQR=Interquartile range

Distress and underlying problems

At T1, 35 survivors (48%) indicated they experienced clinically elevated distress. Twenty-three (32%) reported elevated distress at T2. Eighteen survivors (25%) suffered from clinically elevated levels of distress both at T1 and one year later. Thirty-three (46%) reported low distress at both timepoints (Table 2). The top five most often reported problems were in the physical and emotional domains (Table 3). Fatigue and lack of physical fitness were most often reported at T1 and T2, both by the complete sample and by survivors experiencing continuing elevated distress. Problems were more prevalent in the continuing elevated distress subgroup (e.g. fatigue: N=16/18; 89% (T1)) compared to the complete sample (fatigue: N=48/73; 66% (T1)). The number of survivors who reported one of the top five problems decreased from T1 to T2. At T2, more survivors with continuing elevated distress reported tension/nervousness and fears than at T1.

Variables associated with continuing elevated distress vs. no continuing elevated distress

Time since diagnosis and time since chemotherapy were not related to DT/PL scores at T1 *or* T2 and DT/PL change scores over time. Shorter time since diagnosis was significantly related to a higher likelihood of reporting clinically elevated distress at *both* measurement points i.e. to experience continuing elevated distress (Table 1; r=0.24; small to medium ES). Also, survivors who accessed health care services between diagnosis and T1 (V=0.34; medium ES) and/or between T1 and T2 (V=0.28; small to medium ES) were more likely to report continuing elevated distress (Table 1). Survivors

who had a higher score on the practical (V=0.38; medium to large ES), social (V=0.23; small to medium ES), emotional (V=0.33; medium ES) and/or physical (V=0.47; large ES) problem domains at T1 were more likely to indicate that they experienced continuing elevated distress (Table 2).

Table 2. Descriptives of the DT/PL scores at study entry (T1) and 1 year later (T2), changes over time and univariate associations between the problem domains and continuing elevated distress.

	T1		**T2**		**Continuing elevated distress**
	N (%)	Median (IQR)	*N* (%)	Median (IQR)	*Test statistic (p)*[a]
DT		4.0 (1.5-6.0)		3.0 (1.0-5.0)	
N scoring ≥5	35 (48)		23 (32)		
Elevated distress at T1 and T2			18 (25)		
Low distress at T1 and elevated distress at T2			5 (7)		
Elevated distress at T1 and low distress at T2			17 (23)		
Low distress at T1 and T2			33 (45)		
PL subscales					
Practical (0-70)[r]		4.0 (0.0-11.5)		0.0 (0.0-8.0)	*U*=255.4 (.002)
Social (0-30)[r]		0.0 (0.0-5.0)		0.0 (0.0-1.7)	*U*=371.7 (.050)
Emotional (0-100)[r]		12.0 (3.0-35.0)		9.1 (0.0-22.0)	*U*=279.7 (.005)
Spiritual (0-20)[r]		0.0 (0.0-0.0)		0.0 (0.0-0.1)	*U*=440.1 (.297)
Physical (0-250)[r]		9.5 (9.5-46.5)		7.5 (15.4-34.0)	*U*=181.4 (.000)

[r] = possible scoring range;[a] = Average test result across imputed datasets; *U*=Mann-Whitney *U* test; IQR=Interquartile range.

Table 3. Top 5 distress-related problems at study entry (T1) and 1 year later (T2) for the complete sample and for patients with continuing elevated distress.

	T1				T2			
Rank	**Complete sample**	**(%)**	**Distressed survivors[a]**	**(%)**	**Complete sample**	**(%)**	**Distressed survivors[a]**	**(%)**
1	Fatigue	(66)	Fatigue	(89)	Fatigue	(56)	Lack of physical fitness	(83)
2	Lack of physical fitness	(60)	Lack of physical fitness	(89)	Lack of physical fitness	(49)	Fatigue	(78)
3	Tension/nervousness	(58)	Lack of muscle strength	(78)	Tension/nervousness	(48)	Tension/nervousness	(78)
4	Fears	(56)	Pain	(72)	Sleeping problems	(45)	Fears	(72)
5	Depression	(52)	Tension/nervousness	(67)	Fears	(44)	Sleeping problems	(67)
			Fears	(67)				
			Depression	(67)				
			Concentration problems	(67)				

[a]Survivors who experienced continuing elevated distress defined as a DT score of ≥5 at both T1 and T2.

Referral wish, health care use and actual referral to specific services

Table 4 displays survivors' health care use, referral wish, actual referral at T1 and T2, and uptake of T1 referrals. At T1, 27 survivors considered (37%) and eight (11%) had a referral wish to a psychosocial and/or paramedical health care provider (Table 2). Of these last, two indicated they recently started receiving care for their needs. At T2, 12 considered (17%), and 11 wished (16%) a referral. Two of the eleven had recently been referred (Table 4).

Between diagnosis and T1, supportive care was most often received from a psychologist (N=27; 37%) or a physical therapist/lymphedema therapist (N=18; 25%). The most frequently visited health care providers between T1 and T2 were the physical/lymphedema therapist (N=25; 34%)) and the psychologist (N=10; 14%). At T1, ten survivors (14%) were referred by the research nurse/psychologist after discussion of DT/PL responses, most (N=6) to a psychologist. At T2, 11 (16%) survivors indicated having a referral wish and six (8% of the total group) were referred after discussion of DT/PL responses, three to a gynecologist/sexuologist and three to a psychologist. The one survivor who had been referred to a multidimensional rehabilitation program at T1 actually participated in the program. Of the six survivors referred to a psychologist, three actually went. The two survivors referred to a social worker and the one referred to a gynecologist/sexologist did not uptake the care service.

Table 4. Supportive health care service use, referral wish, actual referral by the research team for T1 and T2 and uptake of T1 referrals (N=73).

	Health care use between diagnosis and T1 (*N* (%))	Referral wish at T1 (*N* (%))[a]	Referred by research team at T1 (*N* (%))		Health care use between T1-T2 (*N* (%))	Referral wish at T2 (*N* (%))[ab]	Referred by research team at T2 (*N* (%))[b]
No	24 (33)	38 (52)	63 (86)		34 (47)	48 (68)	65 (92)
Maybe		27 (37)				12 (17)	
Yes	49 (67)	8 (11)	10 (14)		39 (53)	11 (16)	6 (8)
from/to 1 provider	33 (45)	5 (7)	10 (14)		30 (41)	7 (10)	6 (8)
from/to 2 providers	12 (16)	2 (3)	0 (0)		7 (10)	0 (0)	0 (0)
from/to ≥3 providers	4 (6)	1 (1)	0 (0)		3 (4)	4 (6)	0 (0)
Health care type[c]				Continued	New uptake		
Additional medical or nursing care							
Breast cancer nurse/nurse specialist oncology/nurse practitioner	0 (0)	**2 (3)**	0 (0)	0 (0)	0 (0)	0 (0) **3 (4)**	0 (0)
Gynecologist/sexuologist (total) actual uptake of T1 referral	0 (0)	0 (0)	**1 (1)**	0 (0)	0 (0) 0 out of 1	0 (0) 0 (0)	**3 (4)**
Paramedical health care							
Physical therapist/lymphedema therapist	**18 (25)**	0 (0)	0 (0)	**5 (7)**	**20 (27)**	**1 (1)**	0 (0)
Dietician	0 (0)	**2 (3)**	0 (0)	0 (0)	**3 (4)**	**4 (6)**	0 (0)
Psychosocial health care							
Psychologist (total) actual uptake of T1 referral	**27 (37)**	**7(10)**	**6 (8)**	**7 (10)**	**3 (4)** 3 out of 6	**4 (6)**	**3 (4)**
Social worker (total) actual uptake of referral at T1	**7 (10)**	**1 (1)**	**2 (3)**	**1 (1)**	0 (0) 0 out of 2	**3 (4)**	0 (0)
Psychiatrist	**4 (6)**	0 (0)	0 (0)	**3 (4)**	**2 (3)**	0 (0)	0 (0)

Table 4. (Continued)

	Health care use between diagnosis and T1 (*N* (%))	Referral wish at T1 (*N* (%))[a]	Referred by research team at T1 (*N* (%))	Health care use between T1-T2 (*N* (%))		Referral wish at T2 (*N* (%))[ab]	Referred by research team at T2 (*N* (%))[b]
Pastoral worker	**1 (1)**	0 (0)	0 (0)	**1 (1)**	0 (0)	0 (0)	0 (0)
Other supportive care services							
Multidimensional rehabilitation program (total)	**11 (15)**	0 (0)	**1 (1)**	0 (0)	**4 (6)**	0 (0)	0 (0)
actual uptake of T1 referral					1 out of 1		
Other type of (supportive) health care[c]	**2 (3)**	0 (0)	0 (0)	**1 (1)**	**3 (4)**	**3 (4)**	0 (0)

[a]Survivors who answered 'No' and 'Maybe' on the referral wish question are taken together; [b]Answers from 2 survivors on the referral by the research team question are missing; thus *N*=71 at T2; [c]Both inside and outside the University Medical Center Groningen (UMCG); [d]Other types of health care include: general practitioner, support from fellow patients and creative therapy.

DISCUSSION

This study was the first that longitudinally assessed the DT/PL in breast cancer survivors who were 1 to 5 years after chemotherapy completion and 19 months to 5 years after diagnosis. The findings of the present study are that at least one-third of long-term survivors experienced clinically elevated distress at one of the time points, and one in four survivors reported clinically elevated distress at both time points. This proportion lies well above estimates of psychological morbidity in the general Dutch female population (between 10% and 19%; [34]). The percentage of patients with continuing elevated distress was somewhat higher than the 21% that was reported in a recent Dutch study that used the Dutch DT/PL and included survivors who were 15 months post-diagnosis [17]. This difference may be explained by the treatment modalities survivors received: 63% of survivors in the aforementioned study received radiotherapy only whereas all survivors in the current study received chemotherapy. Patients who (also) receive chemotherapy in contrast to patients who receive other treatment modalities, report higher levels of distress [29,35] and lower emotional functioning at least up to 2 years after diagnosis [36]. The current study shows that a substantial proportion of breast cancer survivors experience *clinically elevated levels* of distress, even beyond the first year after chemotherapy completion.

Fatigue and lack of physical fitness were the most often reported problems as was reported previously [17,28]. Also, the finding that emotional problems such as tension/nervousness and fears were frequently reported was in line with previous research. However, the prevalence of these problems was high compared to previous studies [17,28], especially for emotional problems: other studies with the DT/PL reported percentages of 40% or lower [17,28]. This may again be explained by the fact that all survivors in the current study received chemotherapy. Also, the women in our study were somewhat younger (Mean=50.6; median=52.1) compared to the other studies (Mean=57 [28]; Median=58 [17]) which may explain the higher distress levels [9]. The number of survivors who reported physical and emotional problems decreased over the one-year period but the numbers remained substantial. Also, a higher score for these problems at study inclusion, especially physical problems, increased the likelihood that survivors reported continuing elevated distress. Thus, problems which underlie distress can endure for years after chemotherapy completion in breast cancer survivors. Attention of health care professionals to lingering problems remains important, even years after chemotherapy as these problems and distress may not resolve without additional support.

Our findings show that a large proportion of survivors was or had been using supportive health care services. Notably, the use of a physical/lymphedema therapist increased from 25% to 36% over time. First symptoms of arm lymphedema may occur up to three years after surgery [37,38] and can explain the increase in use of this service. Also, specific problems such as a lack of physical fitness and a lack of muscle strength, which are highly prevalent among survivors in the current study, may have encouraged survivors to seek help from a physical therapist. More than a third of survivors indicated they had received care from a psychologist before they participated in the study. A study including all types of German cancer patients reported that approximately 30% had used psychotherapy and/or psychological counseling since they got cancer. The authors showed that women and patients with symptoms of depression and anxiety were more likely to use these services [39].

The referral wishes survivors reported and consequent referral made by a member of the research team after discussion of the DT/PL did not always align. This could in part be explained by the fact that some survivors recently started receiving care for their needs through self-referral. More importantly, the discussion of DT/PL responses helped survivors to elucidate which problems were most troubling and what type of support was (mostly) needed. Consequently, the wish to be referred to a professional of a certain discipline changed. This result underlines the importance of discussing DT/PL responses as is being recommended in the Dutch guideline on distress management [20].

Our study had a number of limitations. The first is the small sample size. Therefore, we performed univariate analyses to explore associates of continuing elevated distress. Larger samples in future studies are needed to confirm and extend the current results. Second, a large variation existed between the time of chemotherapy completion and the first measurement (between 1-5 years after completion). However, the survivors seem to be a relatively homogeneous group considering the problems and health care use that were reported at both time points. Future research measuring survivors at fixed time-points during the illness trajectory can more precisely indicate survivors' distress, problems, and health care use at specific time-points after chemotherapy completion. Finally, due to our study design, we were not able to assess whether survivors identified with continuing elevated distress experienced these levels of distress during the entire 1-year study period or at the measurement points only nor whether they suffered from elevated distress (at any time) during chemotherapy treatment.

Several important strengths can be noted. The current study was the first to longitudinally examine DT/PL responses in longer-term (breast) cancer survivors, particu-

larly in those who were treated with chemotherapy as they often experience more problems than survivors who received other treatment types [9]. Second, we explored what problem domains were related to continuing elevated distress. One previous study related problem domains to distress but had a cross-sectional design and was performed in lung cancer patients [40]. Third, to the best of our knowledge, this is the first study that made an attempt to explore referral wish as measured with the DT/PL in combination with actual referral and uptake.

Considering the substantial proportion of longer-term breast cancer survivors who report (continuing) elevated distress, distress-related problems and referral wishes, distress screening and management remain important in clinical practice even years after completion of chemotherapy. Physical problems, especially fatigue and lack of physical fitness, were most prevalent and were most strongly related to reporting continuing elevated distress. We recommend to pay special attention to survivors experiencing these problems i.e. to discuss the impact of these problems on survivors' lives, to inform survivors about the potential health risk of not treating these problems and to discuss possible (self-)management strategies for dealing with these distress-underlying problems.

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PART 2

EFFECTS OF WEB-BASED SUPPORT PROGRAMS

CHAPTER 5

Internet-based support programs to alleviate psychosocial and physical symptoms in cancer patients: a literature analysis

Grietje Bouma[a]‡, Jolien M. Admiraal[a]‡, Elisabeth G.E. de Vries[a], Carolien P. Schröder[a], Annemiek M.E. Walenkamp[a], Anna K.L. Reyners[a]

‡ The first two authors contributed equally to the manuscript

[a]Department of Medical Oncology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

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ABSTRACT

In this review the effect of internet-based support programs on psychosocial and physical symptoms resulting from cancer diagnosis and treatment is analyzed. Selection of studies was based on the following criteria: (non-)randomized controlled trials, performed in adult cancer patients, comparing quantitative psychosocial and/or physical outcomes of an internet-based support program with (a) comparison group(s). Literature search yielded 2032 studies of which 16 fulfilled the eligibility criteria.

Three different internet-based support programs were identified: social support groups, online therapy for psychosocial/physical symptoms and online systems integrating information, support and coaching services. Outcomes improved by these programs in nine studies. Especially fatigue, social support and distress improved, regardless of the program type. All online systems showed positive effects, mainly for social support and quality of life. This analysis indicates that internet-based support programs are effective in improving psychosocial and physical symptoms in cancer patients.

INTRODUCTION

A diagnosis of cancer often has a disruptive impact on a patient's life. Cancer patients frequently experience psychosocial and/or physical distressing symptoms [1-3]. The importance of supporting patients adequately regarding symptoms resulting from diagnosis and treatment has been widely recognized [4,5]. However, supportive care needs still go unnoticed frequently [6,7]. To detect and meet the needs of this rapidly expanding patient population, the health care system is urged to develop and employ (cost-) effective programs to educate and support patients.

The internet is a viable medium by which patients can be supported regarding psychosocial and/or physical symptoms. Already in 2007, a Dutch cross-sectional survey on cancer-related internet use demonstrated that 60% of patients frequently used internet by themselves and 9% via others [8], reflecting the high acceptance of internet as a support and information channel. It has important advantages given its wide availability and accessibility, cost-efficiency and ability to provide tailored information and support [8-13]. During the last years, many new eHealth technologies have been introduced in cancer patient care, such as internet-based support programs addressing psychosocial/physical problems, internet-based communication and decision aids to promote shared decision making [14] and mobile applications providing survivorship care plans [15].

Internet-based support programs seem particularly well-suited to fulfill the unmet supportive care needs [4]. These programs have been linked to positive outcomes such as increased knowledge, perceived social support and improved health behaviors for people with chronic diseases [16]. Given the comparable nature of chronic diseases and cancer, these outcomes may also apply to cancer patients [17]. Additionally, several studies showed the feasibility and acceptability of internet-based support programs for both psychosocial and physical symptoms in these patients [4,18,19].

Despite these promising findings, the effects of internet-based support programs specifically designed for cancer patients are less clear. Reviews on the effects of internet-based support programs are scarce in the field of oncology. This paucity is due to the heterogeneous nature of these programs as well as measured study outcomes which renders rigorous evaluation of the effects difficult. The available reviews are either rather broad, for example summarizing all types of internet-based support including non-professional resources [20], or specifically focus on a single type of support program (e.g. online psychological therapy [4]) or tumor type [12]. Also, assessment of study quality has received limited attention. Therefore, the aim of this review was to analyze published clinical trials to assess the effects of internet-based support programs. More specifically,

it was examined whether these programs are capable of alleviating psychosocial and/or physical symptoms resulting from cancer diagnosis and treatment. Additionally, the (methodological) quality of the included studies was evaluated.

METHODS

Eligibility criteria for article selection

Articles were selected based on the following eligibility criteria.

Study design

Eligible studies were randomized controlled trials (RCT) and non-randomized controlled trials (CT), performed in adult cancer patients (≥18 years), comparing quantitative psychosocial and/or physical outcomes of an internet-based support program with (a) comparison group(s). 'Cancer patients' were defined as individuals diagnosed with any solid cancer type, irrespective of disease stage, treatment phase, type of treatment and time since diagnosis. Studies in mixed populations were only included if data for cancer patients were reported separately. Studies must have reported original data. Letters to the editor, patient stories, posters, thesis, review studies and non-English records were excluded.

Internet-based support program

An internet-based support program was defined as any program that aimed to rehabilitate or support cancer patients regarding psychosocial and/or physical symptoms resulting from diagnosis and treatment. Programs that were not primarily designed to support/rehabilitate (e.g. treatment decision aids and health behavior change interventions) were beyond the scope of this review and excluded. Programs focusing exclusively on education were only included if the education aimed to support/rehabilitate cancer patients. The internet-based support program should have been designed by (a) health care professional(s). Studies regarding social support groups were eligible if the groups were moderated by a health care professional. Studies that described programs without access to the internet (e.g. CD-rom or DVD) or to a website (e.g. therapy via e-mail) were excluded.

Outcomes

Quantitative psychosocial (e.g. distress, anxiety, depression, quality of life (QoL)) and physical variables (e.g. fatigue, insomnia, pain and sexual problems) were the outcomes of interest.

Search strategy and selection method

The CINAHL, MEDLINE (PubMed) and PsychINFO databases were searched from in-

ception without limitations. For each database, one review author screened the titles and abstract of the retrieved records. Studies that were identified as clearly nonrelevant were excluded at this stage. Studies that were considered as potentially relevant or as ambiguous regarding eligibility were accessed in full-text and evaluated by two authors independently. The last search was performed on 31-01-2014. The following search terms were used alone or in combination: neoplasm, cancer, carcinoma, oncology, internet, web, online, eHealth, telemedicine, patient education, social support, psycho-education, rehabilitation, support group, support system, therapy, disease management (see Appendix 1 for the full search). The search terms were extensively tested against the output retrieved from initial hand searches. Additionally, reference lists from retrieved articles and relevant systematic reviews were scanned to identify other eligible studies.

Quality assessment

Each included study was assigned a level of evidence according to the Oxford Centre of Evidence Based Medicine [21]. That system distinguishes five levels of evidence ranging from 1 (systematic review of randomized trials; the highest level of evidence) to 5 (mechanism-based reasoning; the lowest level of evidence). Additionally, we assessed the methodological quality of the included studies following a checklist used in a review regarding internet-based interventions in chronic diseases [17], which is an adapted version of the Cochrane Collaboration Back Review Group [22]. We changed the item 'method of randomization explained' into 'randomized groups' as we also included non-randomized CTs. The item on 'assessor blinding' was excluded since it is not feasible to blind the assessor in case of self-report measures. The quality score could range from 0 to 12 points. See Table 3 for the checklist and scoring procedures.

RESULTS

The initial search yielded 2,032 articles and was reduced to 15 original articles (=15 studies) after application of the eligibility criteria. One additional article was identified after examination of the references of included articles and relevant systematic reviews (see Figure 1).

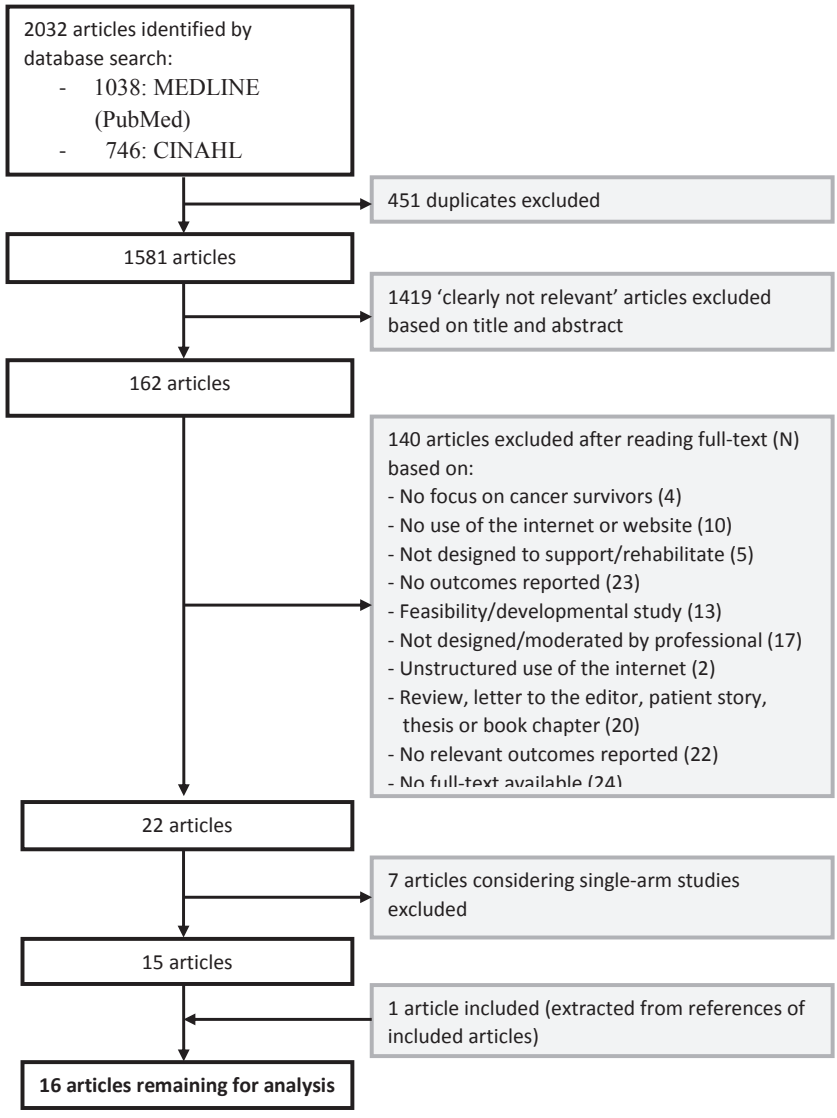

Figure 1. Inclusion process for the literature analysis

Description of selected included studies

Characteristics of the included studies are summarized in Table 1. All studies were published in 2001 or later, with the majority (N=10) being published after 2010. Sample sizes ranged from 27 to 450 participants. All studies had a pre- and post-test design to measure outcome differences in the group(s). Twelve studies were RCTs. Three studies used several experimental [23] or control [10,24] groups, all other studies used a single experimental and control group (e.g. wait-list control, control group receiving usual care). One study examined two different types of programs, i.e. an online therapy for psychosocial symptoms with or without additional use of a support group [25].

Description of participants

The 16 studies comprised 2620 patients. Eight studies focused exclusively on female breast cancer patients. Four studies contained patients with various tumor types [25-28], of which breast cancer patients constituted 39-64%. The remaining studies were performed in patients with prostate [24,29], head and neck [30] and gynecologic cancer [31]. Nine studies included only women and two studies only men [24,29]. The overall median age of the patients was 52 years (range 42-67 years; two studies did not report on age). Seven studies analyzed cancer patients with all disease stages (stage I-IV), whereas four studies only included patients with locally or locally advanced cancer (stage I-III) [24,28,31,32]. Five studies did not specify patients' disease stage [23,29,30,33,34]. Six studies included solely patients who had completed cancer treatment during their follow-up [24-26,28,31,35], one study only included patients during treatment [27] and two studies patients in all treatment phases [30,34]. The remaining studies did not specify patients' treatment phase.

Description of internet-based support programs

Table 2 shows the characteristics of the internet-based support programs. Three different types of programs could be distinguished: social support groups [29,31,33-35], online therapy for psychosocial/physical symptoms [24-26,32] and online systems integrating multiple services such as information, support, communication and coaching services [10,23,27,28,30,36,37]. All but one study [34], provided patient education within the program. The majority of the programs provided the opportunity to communicate with peers [10,23,25,27,29-37] and/or professionals [10,23,24,27,28,30,31,34-37]. Exercises such as cognitive-behavioral homework and coping-skills training were part of the program in five studies [23-26,32]. Except for one internet-based support program [26], all programs were facilitated by a moderator. The moderator's role varied and included fa-

cilitating a discussion and/or introducing new topics in a support group [33,35], being the expert to ask questions [10,23,27,36,37] or having an active role in the intervention such as chatting, discussing and mailing with participants [24,27,30,31,34]. Two studies [28,29] did not describe the role of the moderator. The duration of the programs ranged from 6 weeks to 1 year.

Table 1. Methodological characteristics of the included studies

Program	Experimental (E) and control groups (C)	Target population and sample size	Disease stage	Treatment phase
Online support groups				
Bosom Buddies [33]	E (N=36): Bosom Buddies C (N=36): wait-list control group	Breast cancer patients (N=72) (≤32 months of diagnosis of primary breast cancer)	Not specified	Not specified
GyneGals [31]	E (N=13): GyneGals C (N=14): wait-list control group	Sexually distressed gynecologic cancer patients (N=27) (<5 years post-diagnosis)	Stage I-III	Follow-up
Online cancer support group [34]	E (N=48): internet cancer support group C (N=20): usual care	Spanish-dominant speaking immigrant breast cancer patients (N=68)	Not specified	During treatment and follow-up
Online support group [35]	E (N=24): moderated online support group C (N=26): peer-led online support group (no use of preselected topics or input from a moderator)	Breast cancer patients (N=50)	Stages I-IV	Follow-up: completed treatment ≤32 months
Online support group [29]	E (N=20): educational and support network program C (N=20): wait-list control group, received resource kit including pamphlets	Prostate cancer patients (N=40) (<5 years post-diagnosis, being married/living with significant other)	Not specified	Not specified
Online therapy for psychosocial/physical symptoms				
CAREss (Counseling about regaining erections and sexual satisfaction) [24]	E1 (N=33): internet-based version of CAREss C1 (N=48): wait-list control group C2 (N=40): face-to-face version of CAREss[a]	Prostate cancer patients (N=121) (heterosexual couples with the male partner having undergone localized prostate cancer treatment)	Stages I-III	Follow-up: definitive surgery or radiotherapy between 3 months and 7 years previously
Internet-based coping program [32]	E (N=32): internet-based coping program C (N=30): waiting-list control group	Early stage breast cancer patients (N=62)	Stage 0-III	Not specified
Onward [25]	E (N=15): Onward (Individual Internet Intervention (III) + internet support group) C (N=16): III only	Various cancer patients: breast, lymphoma, lung, colon, sarcoma and thyroid (N=31)	Stages I-IV	Follow up: after completion radiation or chemotherapy
Sleep Healthy Using The Internet (SHUTi) [26]	E (N=14): SHUTi C (N=14): wait-list control group	Patients with any type of cancer and insomnia (N=28)	Stage I-IV (at inclusion in remission)	Follow up: completed active treatment ≥1 month

Table 1. (Continued)

Program	Experimental (E) and control groups (C)	Target population and sample size	Disease stage	Treatment phase
Online systems				
CHESS (Comprehensive Health Enhancement Support System) [23]	E1 (N=118): CHESS information services E2 (N=109): CHESS information + support services E3 (N=111): CHESS information + support + coaching services C (N=112): internet only	Breast cancer patients (N=450) (≤2 months of diagnosis of primary breast cancer or recurrence)	Not specified	Not specified
CHESS [36]	E (N=147): CHESS (full version) C (N=148): received copy of Dr Susan Love's Breast Book	Younger (≤60 years) breast cancer patients (N=295) (<6 months of diagnosis)	Stages I-IV	Not specified
CHESS [37]	E (N=286): CHESS (full version) C (N=51): control group (drawn from a separate RCT)	Low-income breast cancer patients (N=286) (<1 year of diagnosis or metastatic cancer)	Stages I-IV	Not specified
CHESS [10]	E1 (N=91): CHESS (full version) C1 (N=83): internet access + list of high quality breast cancer websites C2 (N=83): books or audiotapes on breast cancer resources	Breast cancer patients (N=257) (<61 days of diagnosis)	Stages I-IV	Not specified
Electronic health information support system [30]	E (N=39): electronic health information support system + standard care C (N=145): standard care	Post-surgery head and neck cancer patients (N=184)	Not specified	During treatment and follow-up
Health Navigation [28]	E (N=136): Health Navigation C (N=137): waiting-list control group	Various cancer patients (breast, stomach, colon, uterine, lung, thyroid) with moderate to severe fatigue (N=273)	Stages I-III	Follow up: completed primary treatment ≤24 months
WebChoice [27]	E (N=162): WebChoice C (N=163): information sheet with suggestions for publicly available cancer-relevant internet sites	Breast and prostate cancer patients (N=325)	Stages I-IV	During treatment

[a] Randomized groups were reported only in the current analysis

Outcomes of included studies

The used measurement instruments and corresponding outcomes of the studies are presented in Table 2. Psychosocial outcome measures, such as (health-related) QoL, depression, distress/stress and perceived social support were the most common used outcome measures. Some studies used validated as well as self-constructed or modified questionnaires [10,23,24,26,28,30,31,33,33,34,36,37].

Positive effects of the internet-based support programs on outcome measures and/or measurement points were reported in nine studies. Of these, seven studies used online systems, one a social support group and one online therapy. Two studies mentioned that the number of included patients was insufficient to detect significant differences [25,31]. Patients in the experimental group experienced a better QoL compared to those in the control group(s) in three studies examining online systems [10,28,30] whereas eight other studies did not report any differences in QoL [23,26,27,29,32,34,36,37]. Two studies found positive effects within the experimental group(s) over time and stable or decreased QoL in the control group, but did not report differences between groups [24,29]. Only one [33] out of seven studies measuring depression found a significant positive effect in favor of the intervention group. A social support group for breast cancer patients resulted in less perceived (post-traumatic) stress [33] and an online system for breast and prostate cancer patients diminished global symptom distress [27]. Other studies using psychological [24,31,32] or sexual distress [31] as outcome measure did not show any effects. Of the six studies having social support as an outcome, three [10,36,37] examining the 'CHESS' program found a positive effect in favor of the intervention group. Programs focusing on cancer-related fatigue [28] and insomnia [26] showed a positive effect on fatigue.

Only three studies examined long term effects (>3 months post-intervention) [10,23,24] of which one had positive long term effects up till 9 months after the end of the intervention on QoL and social support [10].

Quality assessment of included studies

Using the adapted Cochrane list for internet-based interventions, the median total score for methodological quality was 6 (observed range 1-8). The level of evidence based on the Oxford Centre of Evidence Based Medicine together with the (methodological) quality of the included studies is summarized in Table 3.

Table 2. Characteristics of the internet-based support programs and outcomes of the included studies

Program	Description of program	Duration program and measurement points	Outcome measures and measurement instruments	Positive effect(s) for experimental group(s) compared to control group(s)
Online support groups				
Bosom Buddies [33]	Support group moderated by a mental health professional. Weekly, breast cancer related topics were introduced and discussed.	12 weeks. Measures at baseline and 12 weeks.	•Depression: CES-D[e] •Posttraumatic stress disorder: PCL-C[f] •Anxiety: STAI[g] •Stress: PSS[h] •Self-efficacy: CBI[i] •Style of coping with cancer: MINI-MAC[j] •Group experience[a]	+ Depression + Posttraumatic stress disorder + Perceived stress
GyneGals [31]	Asynchronous discussion forum moderated by psychologists and provision of psycho-educational materials addressing psychosocial impact of gynaecologic cancer. Weekly, new topics were introduced.	12 weeks. Measures at baseline and post-intervention.	•Sexual distress: FSDS-R[k] •Anxiety and depression: HADS[l] • Illness intrusiveness: IIRS[m]	No significant outcomes (Study not powered to detect significant differences)
Online cancer support group [34]	Support group moderated by a trained bilingual facilitator. Weekly, issues of interest were discussed.	30 weeks. Measures at pre- and post-intervention.	•Depression: CES-D[e] •Personal growth: PTGI[n,b] •QoL: FACT-B[o,b] •Pain[a]	No significant outcomes

Table 2. (Continued)

Program	Description of program	Duration program and measurement points	Outcome measures and measurement instruments	Positive effect(s) for experimental group(s) compared to control group(s)
Online support group [35]	Support group in a semi-structured (psycho-educational) format using asynchronous communication moderated by a social worker. Weekly, new topics were introduced and discussed.	12 weeks. Measures at baseline, 6, 12 and 16 weeks.	•Depression: CES-D[e]	No significant outcomes
Online support group [29]	Educational and support network program for prostate cancer patients.	6 weeks. Measures at baseline, 6 and 8 weeks.	•QoL: - SF-12v2[p] - EPIC-26[q] - Satisfaction with life scale - Relationship satisfaction questionnaire	No significant outcomes (at 6 weeks: 3 (out of 10) quality of life subscales significantly improved over time)
Online therapy for psychosocial/physical symptoms				
CAREss[c] [24]	Sexual counseling program moderated by therapists. Couples received cognitive-behavioral homework considering sexually-related issues.	12 weeks. Measures at baseline and 12 weeks + 3, 6, 12 months beyond intervention period.	•Sexual satisfaction and function for men: IIEF[r] •Distress:BSI-18[s] •Relationship satisfaction: A-DAS[t]	No formal statistical comparison of E1 with C1/C2 reported (IIEF scores of E1 and C2 improved significantly over time, whereas C1 did not)
Internet-based coping program [32]	Self-guided intervention consisting of coping-skills training exercises, a small discussion board coping group and education on symptom management.	12 weeks. Measures at baseline and 12 weeks.	•Health related QoL: FACT-B[o] and EuroQol-5D "feeling thermometer" •Distress: IES[u] • Physical well-being: MSAS[v]	No significant outcomes

Table 2. (Continued)

Program	Description of program	Duration program and measurement points	Outcomes and measurement instruments	Positive effect(s) for experimental group(s) compared to control group(s)
Online therapy for psychosocial/physical symptoms				
Onward [25]	Program for depression treatment based on cognitive behavioral principles, including an internet support group. Twice a week new lessons and tools were released.	8 weeks. Measures at baseline, 4 and 8 weeks.	•Depressive symptoms: HADS[l]	No significant outcomes (Study not powered to detect significant differences)
SHUTi [26]	Program for improving insomnia symptoms, based on cognitive-behavioral therapy. The program includes 6 interactive cores and a sleep diary.	9 weeks. Measures in 2 weeks before and after intervention.	•Insomnia severity: ISI[w] •Sleep diary: sleep efficiency (SE), total sleep time (TST), sleep onset latency (SOL) •Fatigue: MFSI-SF[x] •Mood: HADS[l] •QoL: SF-12[p]	+ Insomnia severity + SE (subscale sleep diary) + SOL (subscale sleep diary) + Fatigue
Online systems				
CHESS [23]	Home-based system integrating information, support (including discussion groups, 'ask an expert') and coaching services (e.g. for easing distress, healthy relating).	3 months. Measures at baseline, 2 and 6 weeks, 3, 6 and 12 months. (Analysis reported for 6 weeks, 3 and 6 months)	•Emotional processing[a] •Positive coping: Carver's Brief Cope •Functional well-being: FACT-B[o] •Breast cancer concerns: FACT-Bo •Social support: Wisconsin social support scale	6 weeks + Emotional processing (E1>C) + Positive coping (E2>C) 3 months + Emotional processing (E1>C; E2>C)
CHESS [36]	Home-based system integrating information, support and decision services (including health charts, decision aid, action plan).	6 months. Measures at baseline, 2 and 5 months.	•Social support[a] •QoL: FACT-B[o]	5 months + Social support

Table 2. (Continued)

Program	Description of program	Duration program and measurement points	Outcomes and measurement instruments	Positive effect(s) for experimental group(s) compared to control group(s)
CHESS [37]	See description above.	4 months. Measures at baseline and 4 months.	•Perceived social support[a] •QoL: FACT-B[o] •Negative emotion[a] •Health self-efficacy[a]	+ Perceived social support + Negative emotion
CHESS [10]	See description above.	5 months. Measures at baseline, 2, 4 and 9 months.	•QoL: FACT-B[o] •Social support[a]	2 months + QoL (E1>C1) + Social support (E1>C1) 4 months + QoL (E1>C1) + Social support (E1>C1; E1>C2) 9 months + QoL (E1>C2) + Social support (E1>C2)
Electronic health information support system [30]	Electronic health information support system, integrating communication (send messages), information, support (peer-to-peer via forum) and health-monitoring.	6 weeks. Measures at baseline, 6 weeks and 3 months.	•QoL: QoL questionnaire[d]	6 weeks + 5 (out of 22) subscales 3 months + 1 (out of 22) subscale

Table 2. (Continued)

Program	Description of program	Duration program and measurement points	Outcomes and measurement instruments	Positive effect(s) for experimental group(s) compared to control group(s)
Online systems				
Health Navigation [28]	Tailored education program for cancer-related fatigue. Consisting of self-assessment and graphic reports, health advice, online education, enhanced and short message services, caregiver monitoring and support, and health professional monitoring.	12 weeks. Measures at baseline and 12 weeks.	•Cancer related fatigue: BFI[y] and FSS[z] •HRQoL: EORTC QLQ-C30[aa] •Energy conservation: ECSI[ab] •Physical activity: MET[ac] •Nutritional status: MNA[ad] •Psychological distress: HADSl •Pain: BPI[ae] •Sleep quality/quantity: MOSS-SS[af]	+ Cancer related fatigue + Health-related quality of life (only cognitive functional scale)
WebChoice [27]	Interactive health communication application for reducing symptom distress containing an assessment component, tailored symptom self-management support, information section, communication section and a diary.	1 year. Measures at baseline, 3, 6, 9 and 12 months. (analysis for 12 months reported only)	•Symptom distress: MSAS-SF[v] •Depression: CES-D[a] •Self-efficacy: CBI[l] •Health related QoL: 15D-HRQol instrument •Social support: Medical Outcomes Study Social Survey	+ 1 (out of 3) subscale of MSAS-SF (=global distress index)

[a]self-constructed questionnaire by the authors, [b]questionnaire translated by authors, [c] only reporting measurement instruments and outcomes for the male partner,
[d]3 out of 22 subscales were self-constructed
[e]Center for Epidemiological Studies-Depression scale, [f]PTSD Checklist-Civilian version, [g]State-Trait Anxiety Inventory-state scale, [h]Perceived Stress Scale, [i]Cancer Behavior Inventory, [j]MINI-Mental Adjustment to Cancer scale, [k]Female Sexual Distress Scale-Revised, [l]Hospital Anxiety and Depression Scale, [m]Illness Intrusiveness Rating Scale, [n]Posttraumatic Growth Inventory, [o]Functional Assessment of Cancer Therapy-Breast, [p]Short Form Health Survey, [q]Extended Prostate Cancer Index Composite, [r]International Index of Erectile Function, [s]Brief Symptom Inventory-18, [t]Abbreviated form of the Dyadic Adjustment Scale, [u]Impact of Events Scale, [v]Memorial Symptom Assessment Scale(-short form), [w]Insomnia Severity Index, [x]Multidimensional Fatigue Symptom Inventory-Short Form, [y]Brief Fatigue Inventory, [z]Fatigue Severity Scale, [aa]European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C 30, [ab]Energy-Conservation Strategies Inventory, [ac]Metabolic Equivalent of Task, [ad]Mini-Nutritional Assessment questionnaire, [ae]Brief Pain Inventory, [af]Medical Outcome Study-Sleep Scale

Table 3. Quality assessment of the included studies[a,b]

Study	Level of evidence[c]	Methodological quality												Total score
		1	2	3	4	5	6	7	8	9	10	11	12	
Online support groups														
Bosom Buddies [33]	2	√	√	-	√	-	√	√	-	√	-	√	√	8
GyneGals [31]	2	√	√	?	?	-	√	-	-	√	-	√	√	6
Online cancer support group [34]	3	-	-	-	?	-	-	-	-	?	-	?	√	1
Online support group [35]	3	√	-	-	-	√	√	-	-	√	√	?	√	6
Online support group [29]	2	√	√	?	?	-	-	-	-	√	-	?	√	4
Online therapy for psychosocial/physical symptoms														
CAREss [24]	2	√	√	?	?	-	√	√	√	√	-	-	√	7
Internet-based coping program [32]	2	√	√	?	-	-	√	-	-	√	-	-	√	5
Onward [25]	2	√	√	?	-	√	√	-	-	√	-	√	√	7
SHUTi [26]	2	√	√	?	-	-	√	-	-	√	-	√	√	6
Online systems														
CHESS [23]	2	√	√	?	?	-	-	-	√	√	√	?	-	5
CHESS [36]	2	√	√	?	?	-	-	-	-	√	√	√	√	6
CHESS [37]	4	√	-	-	-	-	√	-	-	?	-	√	√	4
CHESS [10]	2	√	√	√	-	-	√	-	√	√	-	√	√	8
Electronic health information support system [30]	3	√	-	-	-	√	√	-	-	√	-	-	√	5
Health Navigation [28]	2	√	√	√	√	-	-	-	-	√	√	√	√	8
WebChoice [27]	2	√	√	?	√	-	√	-	-	√	√	√	√	8

[a] 1= Specification of eligibility criteria, 2= randomized groups, 3= treatment allocation concealed, 4= groups similar at baseline, 5= explicit description of interventions, 6= description of compliance, 7= description of dropout and comparison with completers, 8= long-term follow-up (>3 months after post-intervention assessment), 9= timing of outcome assessment comparable, 10= sample size described with power calculation, 11= intention-to-treat analyses, 12= point estimates and measures of variability.

[b] √ = reported item or yes (1 point), - = unreported item or no (0 points), ? = unclear item or unable to determine (0 points). Total score can be 12.

[c] Level of evidence according to the system used by the Oxford Centre for Evidence-Based Medicine.

DISCUSSION

The most apparent result from this review is that the majority of the included studies reported positive effects on patient-reported psychosocial and physical symptoms, regardless of the used program type. This result differs from a similar review conducted in 2010 [20]. That review focused on empirical studies (N=24 including 37 articles) reporting outcomes of the use of online support/resources by adult cancer survivors. The authors concluded that use of online support/resources showed promising but inconclusive evidence for positive outcomes due to a lack of rigorous evaluations. In the current review rather strict criteria for the final inclusion for analysis of studies were used. For example, only (non-)randomized controlled trials focusing on professionally designed internet-based programs for cancer patients were included. As a result, only five studies included in the previous review met our inclusion criteria. Moreover, our review includes ten studies published since 2010, of which six reported positive outcomes.

Comparable reviews analyzing studies conducted in patients with chronic diseases also showed positive effects of internet-based support programs. A recent systematic review included 17 studies examining online mental health interventions in patients with chronic gastrointestinal conditions. That review showed that these online interventions resulted in less somatic symptoms and an improved quality of life [38]. Another systematic review in patients with various chronic diseases including diabetes, heart failure and COPD (N=18 RCTs) found beneficial effects of internet-based interventions on patient empowerment [17]. A Cochrane systematic review involving 24 RCTs including in total 3739 patients with chronic diseases found a positive effect of online systems on perceived social support [16]. This finding is in line with our review that showed positive effects for all online systems, mainly for the outcome social support. Given these findings, online systems may well be a generic tool to support patients with various diseases, in different disease stages and treatment phases.

The supportive care needs of cancer patients may differ depending on their socio-demographic and illness-related characteristics. For example, several studies reported that supportive care needs vary by age [39-41]. Therefore, it has been recommended that interventions fit the characteristics and needs of recruited patients [4]. In the current review, patients' median age was relatively young (52 years) compared to the median age of cancer patients at diagnosis which is 66 years [42]. The majority of the studies included in this review focused on breast cancer patients. Whether internet-based support programs should be adapted to age groups and/or tumor types to

optimize effectiveness is unclear. Happily, several ongoing trials will shed light on this aspect as studies are ongoing in patients with tumor types such as prostate cancer, lung cancer and neuroendocrine tumors (ClinicalTrials.gov Identifiers NCT01716702, NCT01012401, NCT01849523) [43].

Our methodological quality assessment showed that the included studies could have been improved on several aspects in order to obtain a higher quality level. For example, in 14 of the 16 studies, study completers were not compared with drop-outs. This comparison may provide valuable information regarding which patients benefit from the internet-based support programs. Twelve of the included studies were conducted in the US. Caution is warranted in generalizing these results to patients in other countries because of possible differences in health care systems and expectations of the role of health care professionals as noted by the aforementioned Cochrane review [16].

A few limitations could be noted regarding our review. The included studies made use of many different outcomes. This heterogeneity hampers firm conclusions regarding effects on some less frequently studied outcomes. Also, some included studies had small sample sizes (e.g. [25,31]). The absence of significant effects might be caused by a lack of power instead of true ineffectiveness of the intervention.

Since cancer patients make widespread use of internet-based technologies, the challenge is to provide easy accessible tools that will be of benefit for the individual patient. Internet-based technologies appear at a much greater pace than research can keep up with. A way to resolve this challenge is to examine the efficacy of generic program components and/or underlying principles that are more timeless than the programs themselves as has been proposed previously [44]. Successful implementation into routine cancer care represents another challenge but is crucial to reach the full potential of internet-based support programs. A barrier for patients might be a lack of accessible internet-based support programs that match their supportive care needs and preferences. Patient preferences for internet-based support vary considerably as demonstrated by a recent study on use patterns of the online system 'WebChoice' [45]. It cannot be expected that a few accessible programs will cover the supportive care needs of all patients. We recommend that more effort should be put in the disclosure of available web-based support programs and tools. For example, a portal website could be constructed which contains all available supportive care programs/tools including apps, websites and social media for cancer patients. As such, patients are provided with a choice what type of supportive care programs/tools matches their need and preferences. Ultimately, patients will receive the supportive care they wish for and benefit from the wealth of tools and programs delivered through the internet.

Conflict of interest statement

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APPENDIX 1. FULL SEARCH DATABASES

MEDLINE (PubMed)

(((Neoplasms[MESH] OR Carcinoma[Mesh]) OR (cancer*[TIAB] OR neoplasm*[TIAB] OR carcinoma*[TIAB] OR oncology[TIAB])) AND ((Internet[Mesh] OR web*[TIAB] OR online*[TIAB] OR internet*[TIAB]) OR (e-health*[TIAB] OR eHealth*[TIAB]) OR (telemedicine[MESH:noexp])) AND ((“Patient Education as Topic”[Mesh]) OR (“Social Support”[Mesh]) OR (psychoeducat*[tiab]) OR (“rehabilitation”[MESH]) OR (support group*[tiab]) OR (support system*[tiab])))

CINAHL

(((MH “Neoplasms+”) OR (MH “Oncology+”) OR TI (“cancer*” OR “neoplasm*” OR “carcinoma*” OR “oncology”) OR AB (“cancer*” OR “neoplasm*” OR “carcinoma*” OR “oncology”)) AND ((MH Internet+ OR MH telehealth+) OR TI (“internet*” OR “web*” OR “online*” OR “e-health*” OR “eHealth*”) OR AB (“internet*” OR “web*” OR “online*” OR “e-health*” OR “eHealth*”)) AND ((MH “Patient education”) OR (MH “Support, psychosocial”) OR (MH “Psychoeducation”) OR (MH “Rehabilitation, Cancer”) OR (TI “support group*”) OR (TI “support system*”) OR (AB “support group*”) OR (AB “support system*”)))

PsychINFO

(((DE “Neoplasms”) OR (DE “Benign Neoplasms”) OR (DE “Breast Neoplasms”) OR (DE “Endocrine Neoplasms”) OR (DE “Nervous System Neoplasms”) OR (DE “Terminal Cancer”) OR TI (“cancer*” OR “neoplasm*” OR “carcinoma*” OR “oncology”) OR AB (“cancer*” OR “neoplasm*” OR “carcinoma*” OR “oncology”)) AND ((DE “Internet”) OR (DE “Telemedicine”) OR TI (“internet*” OR “web*” OR “online*” OR “e-health*” OR “eHealth*”) OR AB (“internet*” OR “web*” OR “online*” OR “e-health*” OR “eHealth*”)) AND ((DE “Client Education”) OR (DE “Support Groups”) OR (DE “Psychoeducation”) OR (DE “Online Therapy”) OR (DE “Disease Management”) OR (DE “Rehabilitation”) OR (DE “Cognitive Rehabilitation”) OR (DE “Neuropsychological Rehabilitation”) OR (DE “Neurorehabilitation”) OR (DE “Occupational Therapy”) OR (DE “Physical Therapy”) OR (DE “Psychosocial Rehabilitation”) OR TI (“rehab*” OR “support system*” OR “support group*” OR “patient educat*”) OR AB (“rehab*” OR “support system*” OR “support group*” OR “patient educat*”)))

CHAPTER 6

Web-based tailored psycho-education for breast cancer patients at the onset of the survivorship phase: a multicenter randomized controlled trial

Jolien M. Admiraal, MSc[1]; Annette W.G. van der Velden, MD[2]; Jenske I. Geerling, NP[1a]; Johannes G.M. Burgerhof, MSc[1b]; Grietje Bouma, MD[1a]; Annemiek M.E. Walenkamp, MD, PhD[1a]; Elisabeth G.E. de Vries, MD, PhD[1a]; Carolien P. Schröder, MD, PhD[1a], Anna K.L. Reyners, MD, PhD[1a]

[1]University of Groningen, University Medical Center Groningen, Groningen, the Netherlands
[a]Department of Medical Oncology
[b]Department of Epidemiology
[2]Department of Medical Oncology, Martini Hospital, Groningen, The Netherlands

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ABSTRACT

Context: Many breast cancer patients have unmet informational and psychosocial needs after treatment completion. A psycho-educational intervention may be well-suited to support these patients.

Objectives: The purpose of this multicenter randomized controlled trial was to examine the effectiveness of a web-based tailored psycho-educational program (ENCOURAGE) for breast cancer patients which aims to empower patients to take control over prevailing problems.

Methods: Female breast cancer patients from two hospitals in the Netherlands who recently completed (neo-)adjuvant chemotherapy were randomly assigned to standard care or 12-week access to the ENCOURAGE program providing fully automated information, problem-solving strategies, resources and services for reported problems. At 6 and 12 weeks, patients completed self-report questions on optimism and control over the future (primary outcome), feelings of being informed and acceptance of the illness. At baseline and 12 weeks, distress and quality of life questionnaires were completed.

Results: 138 patients were included. Almost all patients (67/69) visited ENCOURAGE as requested. No differences between the control and the intervention group were observed for primary and secondary outcomes. An unplanned subgroup analysis showed that in clinically distressed patients (N=57 at baseline; 41%), use of the ENCOURAGE program increased optimism and control over the future at 12 weeks more than in patients in the control group (Cohen's *d*=0.65).

Conclusions: Although the effectiveness was not demonstrated, a subgroup of women treated for breast cancer can probably be supported by the program. The results of the current study are a starting point for further development and use of the program.

INTRODUCTION

The presence of psychosocial and physical symptoms after completion of breast cancer treatment is well-known [1-3]. Patients struggle with psychological issues as well as physical symptoms [4,5]. Many patients wish for information about symptoms/problems that may arise after treatment completion and about strategies how to cope with these problems [1,6]. However, interventions that focus on supporting breast cancer patients during the first year after primary treatment completion (i.e. re-entry phase) are scarce [7-9]. Psycho-education, which combines patient education with activities such as advice on self-management strategies and/or counseling [10,11], may be well-suited to support patients during the re-entry phase. The few psycho-educational interventions that focused on breast cancer patients in the re-entry phase - delivered in multi-sessions via group, face-to-face and/or video format - showed positive effects on outcomes such as anxiety, depression, fatigue and quality of life [12-14]. Benefits were also found for a brief 2-hour psycho-educational group session regarding knowledge and preparedness for the re-entry phase [8]. These interventions required involvement of (a) health care professional(s) and, therefore, were relatively labor intensive. Considering the growing number of breast cancer survivors, the internet has been viewed as a cost-effective medium to support patients [15]. New web-based programs emerge at a rapid pace [16], but only few web-based interventions for breast cancer patients in the re-entry phase are available at present.

Therefore, we developed the ENCOURAGE program. This is a web-based tailored psycho-educational program for breast cancer patients in the re-entry phase which aims to empower patients to take control over prevailing problems and to adjust to life after treatment. We adopted a problem-solving orientation in the development of ENCOURAGE. This orientation involves appraising problems as challenges, be optimistic about the solvability of problems and having a sense of personal control over the problems [17]. According to the theory of problem solving, when patients learn to identify and solve problems, their sense of control and confidence will increase and these changes will in turn enhance adjustment [18,19]. Additionally, research showed that the use of active approach-oriented coping strategies (e.g. emotional expression, seeking social support) is related to perceived control and enhances healthy adjustment to cancer [20-24]. The possible solutions to a problem offered by ENCOURAGE emphasize the use of approach-oriented coping strategies.

A randomized prospective study was performed to measure the effects of the ENCOURAGE program. We hypothesized that breast cancer patients who use the program

report a larger increase in optimism and feelings of control over the future than patients who receive standard care. Patients' feelings of being informed, acceptance of the illness, distress and quality of life were also studied.

METHODS

Patients

Patients were recruited at the outpatient clinics of Medical Oncology Departments between January 2013 and October 2014 in two hospitals in the North-Eastern part of the Netherlands: the Martini Hospital (MH, Groningen) and the University Medical Center Groningen (UMCG, Groningen). The study was approved by the medical ethical committee and was registered (ClinicalTrials.gov, Identifier NCT01834521). Informed consent was obtained from all included patients. Female breast cancer patients diagnosed with primary breast cancer who completed curative-intent primary treatment within the past 6 months (defined as surgery combined with any type of (neo)adjuvant chemotherapy) were eligible. Patients might still be receiving immunotherapy, hormonal therapy and/or radiotherapy.

Other inclusion criteria were: ≥18 years of age, ability to comprehend Dutch reading and writing, having access to the internet including an e-mail address (at home or via family/friends) and physically and cognitively able to participate. Patients were not eligible when they were diagnosed with recurrent and/or metastasized breast cancer.

Procedures

This was a prospective, randomized controlled, multi-center, parallel-group study. Patients who were identified as eligible received a study information letter, an informed consent form, the baseline questionnaire (T0), an address form, two general information leaflets ('Breast cancer' and 'Continuing life after cancer' of the Dutch Cancer Society) and a prepaid return envelope. Patients who did not return the documents within two weeks received a reminder call.

After receiving the returned documents, patients were randomized between standard care (control group) or access to the ENCOURAGE program (intervention group) by a data-manager of the UMCG. The patients were allocated with a computer-generated randomization list using blocked randomization to conceal the allocation sequence until intervention assignment (allocation ratio 1:1; block size of 4; stratified per hospital). Patients were informed by phone by the research psychologist about the randomization outcome. Blinding of patients or the research team was not applied.

Patients received questionnaires at 6 (T1) and 12 weeks (T2) by mail. If questionnaires were not returned after 1 week, patients received a reminder e-mail. Patients were contacted by telephone if they did not respond within 1 week after the reminder.

Intervention and control condition

Key features of ENCOURAGE (http://lastmeter.medischeoncologiegroningen.nl; username: JPainSymptomManage; password: Symptom1; Appendix 1) were inspired on problem-solving therapy [17,18]: 1) *Problem orientation and identification:* an online version of the Dutch Distress Thermometer (DT) and accompanying 47-item Problem List (PL) covering practical, family/social, emotional, religious/spiritual and physical problems [25] was used to identify the problems patients experienced. After completion, patients immediately received online feedback about their distress score. The feedback identified three levels of distress severity (DT=0-4 for no or mild distress; DT=5-7 moderate distress and DT=8-10 severe distress [25]); 2) Subsequently, patients received fully automated *tailored psycho-education* for the reported problems. Psycho-educational material was written for 30 problems separately, from a re-entry specific viewpoint (Appendix 2[2]). Psycho-education comprised background information about problems (including normalization), possible problem-solving strategies for coping, resources including hyperlinks to other websites and services (for self-referral). Completed DT/PL's were automatically saved online to ensure access to the psycho-educational material any time later. All DT/PLs that were (partly) completed by patients were registered for study purposes. Program content was fixed during the 12 weeks. Patients could contact the research psychologist (telephone/e-mail) to discuss any questions and/or roblems.

The content of the ENCOURAGE program was based on contemporary scientific literature and input from a multidisciplinary team of psychologists, oncology nurses, medical oncologists, a pastoral worker and a patient advocate. Breast cancer patients within 9 months after chemotherapy completion from the UMCG (N=12) evaluated the content of the program positively in terms of usefulness (Cohen's *d*=0.30), feeling informed (0.66) and increased optimism and control over the future (0.96) in a small single arm pilot study compared to patients >9 months after chemotherapy (N=7).

Patients assigned to the intervention group, had access to the program during 12 subsequent weeks. An e-mail was sent to patients containing a leaflet that introduced the ENCOURAGE program together with log-in information. Patients were requested to visit the program and to complete the online DT/PL at least once during the first 7 days after receiving login information to ensure that all participants received some amount of psycho-educational material. The research psychologist contacted patients that had not accessed the program within the first week (a reminder mail was send, after 2 weeks they received a telephone call). No further use requests were imposed.

2 Appendix 2 can be found in appendix A in this thesis

Standard care consisted of regular visits to a medical specialist (medical, surgical or radiation oncologist and/or oncology nurse) every 3 or 4 months during the first follow-up year. Patients were referred to additional health care by their oncologist and/or oncology nurse in case of unmet needs and/or a referral wish.

Measures

At baseline (T0), patient characteristics, health care use, distress and quality of life were assessed. At 6 (T1) and 12 weeks (T2) optimism and control over the future, feeling informed and acceptance of the illness, were measured. At 12 weeks (T2) patients' health care use, distress and quality of life were re-assessed. At T2, the intervention group also received a questionnaire regarding website opinion and use (T2).

A self-report questionnaire was used to assess socio-demographic characteristics. Illness-related characteristics and treatment received were collected from patients' medical records. The questionnaire also asked whether psychosocial and/or paramedical health care had been used before breast cancer diagnosis, after diagnosis and/or during study enrollment.

Increased optimism and control over the future' (primary outcome) is an 8-item subscale (Cronbach's alpha=0.75 (T1); alpha=0.79 (T2)) of the 'Constructs Empowering Outcomes' (CEO) questionnaire [26]. This questionnaire is developed and tested in various online support groups including breast cancer patients [27,28]. The subscales 'feel better informed' (4 items; alpha=0.94; alpha=0.94) and 'improved acceptance of the illness' (5 items; alpha=0.92; alpha=0.94) were also measured. The questionnaire assesses retrospectively to what extent patients experience certain outcomes by their participation in an online support group. We changed 'online support group' into 'website' and 'information leaflets' for the intervention and control group, respectively. All items began with the statement: 'Through the use of the website/information leaflets…'. Patients could answer on a 5-point scale ranging from 'completely disagree' (1) to 'completely agree' (5). For each subscale a mean total score was calculated. Total scores were not calculated for the CEO questionnaire as the subscales measure heterogeneous constructs [27].

Distress was measured using the Dutch DT/PL [25,29]. The DT consists of a single item that asks patients to indicate the amount of distress experienced during the past week on an 11-point scale (0-10; no to extreme distress). On the 47-item PL, patients could indicate whether or not (yes/no) they experienced certain problems. Patients were asked to rate from 1-10 the amount of distress they experienced for each item in the PL they answered 'yes'. Lastly, the questionnaire measures patients' referral wish (yes, maybe or no) to a health care professional.

Quality of Life (QoL) was measured using the EORTC QLQ-C30, version 3.0 [30] and the QLQ-BR23 [31]. Global health status/QoL and the functional scales of these questionnaires (physical, role, cognitive, emotional, social functioning and body image, sexual functioning, sexual enjoyment and future perspective) were included.

The Technology Acceptance Model (TAM) questionnaire [32] was used to assess patients' opinion of the ENCOURAGE program. The subscales 'perceived usefulness' (3 items, alpha=0.94), 'positive attitude' (1 item) and 'actual usage' (1 item) were assessed. Items are rated on a 5-point Likert scale, ranging from 'completely disagree' (1) to 'completely agree' (5). At the end of the questionnaire, patients had the opportunity to comment on the program in free text format.

Data analysis

The power analysis was performed on the difference for the mean subscale score of 'increased optimism and control over the future' between the control and intervention group at 12 weeks (T2). We aimed to recruit 128 patients (64 in each group) to detect a medium effect size of 0.50 using a two-tailed test (β=0.80; α=0.05 (G*power [34])). Recruitment continued until 128 patients returned the T2 questionnaire.

The range of missing values was 0.0%-13.8% for all variables except for distress at T2. This variable had 24.6% missing values. Missing data patterns were examined and subsequently multiple imputed (20 imputations) by use of the fully conditional specification algorithm [35,36]. The results of the complete case analyses were similar to the results of the imputed datasets (N=138). Therefore, we decided to report the results based on the analyses of the original data.

Descriptive statistics were calculated for socio-demographic and illness-related characteristics, CEO scales, TAM scales, QoL, the DT/PL and health care use. Analyses were performed according to the intention-to-treat principle. Separate ANCOVAs were performed to examine the effect of study group on the CEO scales and on changes in the DT/PL and QoL domains from baseline to T2. Differences between the study groups in patient characteristics, health care use and/or baseline measures were included as covariates in the ANCOVA models. Separate ANCOVA analyses were performed for clinically distressed breast cancer patients. Patients were defined as clinically distressed with a baseline DT score ≥5 [25,37]. These subgroup analyses were unplanned and therefore, underpowered. If standardized residuals of the ANCOVA model were non-normally distributed, the outcome variable was dichotomized (stable/improved scores versus worsened scores) and analyzed by a logistic regression analysis. Effect sizes were calculated by Cohen's *d* for independent groups (mean unadjusted difference between the study groups divided by the pooled standard deviation). Statistical analyses were performed by SPSS (v23; SPSS Inc. Chicago, IL).

RESULTS

Patient characteristics

Of the approached 207 patients, 139 were enrolled in the study between January 2013 and October 2014. Figure 1 displays the CONSORT diagram. Patients not interested to participate most often reported that they were too busy or did not want to be confronted with cancer-related information. Characteristics of the patients in the control and the intervention group are provided in Table 1. Less patients in the control group received immunotherapy during the study period than patients in the intervention group (χ^2=4.0, *P*=.047). No differences between study completers and dropouts were observed for the baseline measures.

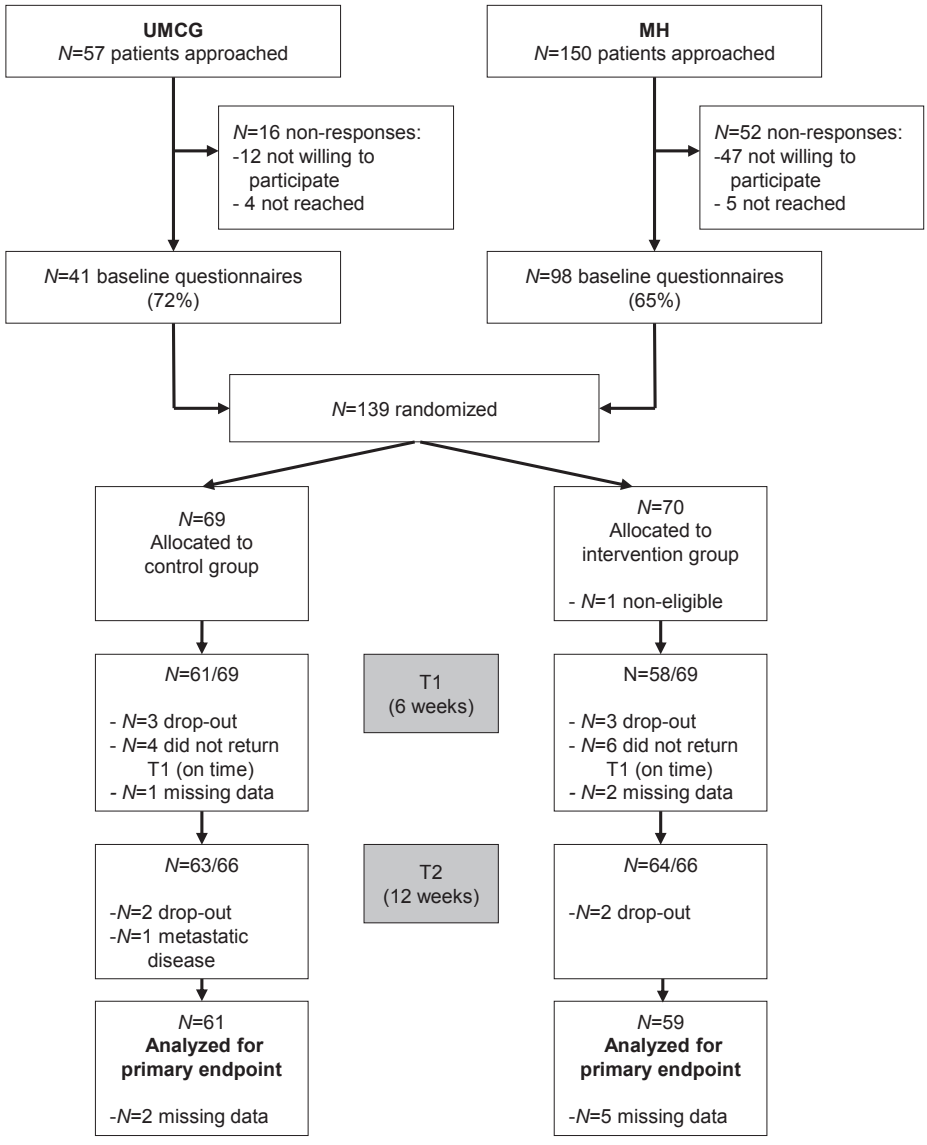

Figure 1. CONSORT diagram of patient flow from patient approach to analyses. UMCG: University Medical Center Groningen; MH: Martini Hospital

Table 1. Patient characteristics at baseline (*N*=138).

	C		I		
	N	***M ± SD***	***N***	***M ± SD***	**P**
Age (years)	69	53.2 ± 8.5	69	53.1 ± 9.8	.920
Time since diagnosis (months)	69	8.7 ± 1.9	69	8.7 ± 2.1	.920
Time since chemotherapy (months)	69	2.4 ± 1.7	69	1.9 ± 1.5	.078
	C		I		
	N	%	*N*	%	*P*
Marital status					.429
Married/living together	50	73	54	78	
Single/widowed/divorced/LAT	19	28	15	22	
Children					.477
Yes	57	83	60	87	
No	12	17	9	13	
Children at home					.125
Yes	29	42	38	55	
No	40	58	31	45	
Educational level					.298
Lower vocational	4	6	5	7	
Secondary education/higher general	32	46	40	58	
Higher vocational/University	33	48	24	35	
Employment					.168
Yes	44	64	36	52	
No	25	36	33	48	
Cancer stage					.561
I	33	48	30	44	
II	1	1	3	4	
III	35	51	36	52	
Breast cancer type					.477
IDC	54	78	58	84	
ILC	10	15	9	13	
Other	5	7	2	3	
Surgery					.733
Lumpectomy	35	51	33	48	
Mastectomy	34	49	36	52	
Cancer treatment during study					
Cosmetic surgery[a]					.546
Yes	7	10	5	7	
No	62	90	64	93	

Table 1. (Continued)

	C		I		
	N	%	*N*	%	*P*
Radiotherapy[a]					.066
Yes	11	16	20	29	
No	58	84	49	71	
Immunotherapy[a]					**.047**
Yes	8	12	17	25	
No	61	88	52	75	
Hormone therapy					.848
Yes	51	74	50	73	
No	18	26	19	28	
Health care use					
Before diagnosis					.488
Yes	26	38	30	43	
No	43	62	39	57	
After diagnosis					.725
Yes	42	61	44	64	
No	27	39	25	36	
During study					.145
Yes	42	67	34	54	
No	21	33	29	46	

M=mean; SD=standard deviation; I=intervention group; C=control group; ns=non-significant
Indepent-samples t-tests (continuous variables) and X^2 tests (categorical variables) were used to examine differences between study groups.

Use and evaluation of the ENCOURAGE program

According to the log files, two patients never visited the program. One of these patients returned the questionnaires and the intention-to-treat principle was applied. Eighteen patients did not log in within 1 week and were reminded by e-mail. Seven patients received an additional phone call as they had not logged in after 2 weeks. These contacts focused on program access and support was only provided for technical issues. The number of online DT/PLs patients started, ranged from 0-7 (median=2; N=69), with 61% of the patients logging in more than once. Self-reported use of the program was similar to this usage statistic (range 0-6; median=2; N=62).

The mean score patients assigned to the usefulness of the program was 3.55 (SD=0.89; N=59). Of the patients, 71% agreed (score=4) or completely agreed (score=5) with having a positive attitude towards the program. Ten percent was not satisfied with the program.

Three patients contacted the research psychologist to discuss problems and/or

health care needs. The number of problems reported on the online DT/PLs ranged from 0 to 30 (M=14; SD=6). Psycho-education was provided most often (89x) for 'lack of physical fitness' (73% of total number of completed PLs)), 'fatigue' (71%), 'problems with appearance' (56%), 'tingling in hands/feet' (55%) and 'lack of muscle strength' (55%).

Primary and secondary outcomes

No significant difference was detected in 'increased optimism and control over the future' at T2 between the control and the intervention group. Also, no effects were detected for the primary outcome at T1. Patients in the control group reported higher scores for 'being better informed' and 'increased acceptance' than patients in the intervention group at T1. At T2, no differences between the study groups for these outcomes were obtained (Table 2). Both study groups improved equally well between T1 and T2 regarding 'increased optimism and control over the future', 'being better informed', and 'increased acceptance'. Improvements in distress, distress-related problems and QoL were observed in both study groups but no significant differences were observed between the groups at T2 (Table 3).

Distressed breast cancer patients

Several patients reported that they did not felt supported by the ENCOURAGE program since they did not experience high distress for which they needed additional support. Therefore, we decided to analyze the 57 (41%) clinically distressed patients separately (*N*=21 in the intervention group, *N*=26 patients in the control group, *N*=10 missing data at T2).

Usefulness of the program was rated with a 3.75 (SD=0.75; N=21). Seventeen of 21 distressed patients (81%) randomized in the intervention group agreed or completely agreed with having a positive attitude towards the program. More distressed patients in the intervention group (15%) than in the control group (38%) received radiotherapy during the study period (χ^2=3.15, p=0.076, N=47).

The clinically distressed patients in the intervention group reported a higher increase in optimism and control over the future at T2 than the patients in the control group (Table 2). Additionally, in the intervention group (M_{change}=0.25), but not in the control group (M_{change}=0.02), 'increased optimism and control over the future' improved from T1 to T2 (95% CI=0.06-0.58, F(1,40)=6.31, P=.016, Cohen's d=0.51). No between-group effects were observed for the secondary outcomes (Table 3).

Table 2. Group means and differences for empowering outcomes for the control and intervention group.

	At 6 weeks (T1)							At 12 weeks (T2)						
	C		I		Group differences			C		I		Group differences		
CEO subscale	*M ± SD*	*N*	*M ± SD*	*N*	*I – C (95% CI)[ab]*	*P[ab]*	*ES*	*M ± SD*	*N*	*M ± SD*	*N*	*I – C (95% CI)[ab]*	*P[ab]*	*ES*
Complete sample														
Increased optimism and control	3.09 ± 0.54	61	3.14 ± 0.50	58	0.06 (-0.13, 0.26)	.515	0.11	3.10 ± 0.57	61	3.18 ± 0.52	59	0.10 (-0.10, 0.30)	.312	0.15
Being better informed	3.73 ± 0.57	60	3.39 ± 0.82	58	-0.31 (-0.57, -0.05)	.020	0.48	3.56 ± 0.65	62	3.31 ± 0.86	60	-0.24 (-0.52, 0.04)	.088	0.33
Improved acceptance	3.09 ± 0.88	61	2.78 ± 0.79	58	-0.32 (-0.63, -0.01)	.044	0.37	3.04 ± 0.90	62	2.73 ± 0.88	60	-0.26 (-0.58, 0.06)	.114	0.35
Distressed patients														
Increased optimism and control	3.03 ± 0.59	26	3.10 ± 0.61	22	0.08 (-0.28, 0.44)	.666	0.11	2.97 ± 0.57	26	3.34 ± 0.59	21	0.43 (0.85, 0.78)	.017	0.65
Being better informed	3.69 ± 0.65	25	3.44 ± 0.90	22	-0.27 (-0.74, 0.20)	.246	0.31	3.49 ± 0.69	27	3.38 ± 0.86	22	-0.13 (-0.62, 0.35)	.584	0.15
Improved acceptance	3.13 ± 0.97	26	2.85 ± 0.80	22	-0.32(-0.85, 0.22)	.236	0.32	2.96 ± 0.93	27	3.08 ± 0.77	22	0.08 (-0.43, 0.59)	.751	0.14

M=mean; SD=standard deviation; C=control group; I=intervention group; ES=effect size

[a]Complete sample=adjusted for the variable 'receiving current immunotherapy'; [b]Distressed patients=adjusted for the variable 'receiving current radiotherapy'

Table 3. Group means and differences for distress, distress-related problems and QoL for the control and intervention group.

	Baseline (T0)				Δ12 weeks (T2)				
	C		I		C	I	Group differences		
Outcome	*M ± SD*	*N*	*M ± SD*	*N*	*M ± SD*	*M ± SD*	*Δ I - C (95% CI)* [ab]	*P* [ab]	*ES*
Complete sample									
Distress									
DT	4.65 ± 2.00	51	3.82 ± 2.24	49	-0.59 ± 2.55	-0.20 ± 2.15	-0.02 (-0.91, 0.87)	.964	0.16
Problem domains									
Practical	0.74 ± 0.96	63	0.81 ± 1.05	61	-0.16 ± 1.03	-0.25 ± 1.16	0.96 (0.39, 2.38)[c]	.936	
Social	0.30 ± 0.99	62	0.51 ± 1.09	62	0.04 ± 1.22	-0.27 ± 0.84	5.08 (0.49, 52.58)[c]	.173	
Emotional	1.38 ± 1.30	58	1.48 ± 1.72	58	-0.08 ± 1.32	-0.34 ± 1.41	-0.27 (-0.68, 0.14)	.190	0.19
Spiritual	0.52 ± 1.31	61	0.54 ± 1.48	61	-0.24 ± 1.19	-0.37 ± 1.11	0.76 (0.11, 5.39)[c]	.787	
Physical	1.53 ± 1.18	60	1.45 ± 1.15	57	-0.64 ± 1.02	-0.58 ± 1.01	-0.06 (-0.28, 0.16)	.588	0.06
QoL – EORTC-C30									
Global health status/QoL	67.46 ± 18.74	63	68.55 ± 17.56	62	5.95 ± 17.67	5.78 ± 19.42	0.90 (-4.33, 6.12)	.735	0.01
Functional scales									
Physical	76.83 ± 16.76	63	79.68 ± 17.64	62	9.21 ± 13.52	6.42 ± 15.33	-0.61 (-4.42, 3.21)	.754	0.19
Role	63.23 ± 27.62	63	66.94 ± 29.18	62	11.11 ± 25.92	9.68 ± 25.53	2.44 (-4.70, 9.57)	.500	0.06
Emotional	82.01 ± 17.91	63	80.03 ± 19.83	63	1.41 ± 17.26	2.29 ± 19.06	0.08 (-5.22, 5.39)	.976	0.05
Cognitive	75.93 ± 18.64	63	79.37 ± 21.53	63	5.03 ± 14.86	3.97 ± 20.02	2.28 (-2.77, 7.33)	.374	0.06
Social	76.19 ± 27.55	63	77.96 ± 22.34	62	8.47 ± 25.38	11.02 ± 20.46	4.24 (-1.63, 10.10)	.155	0.11
QoL – BR23									
Body image	77.42 ± 22.55	62	69.53 ± 25.77	64	5.11 ± 15.63	11.46 ± 23.03	2.91 (-3.05, 8.78)	.335	0.32
Sexual functioning	20.43 ± 21.00	62	14.41 ± 18.94	59	6.45 ± 15.78	8.47 ± 15.59	0.52 (-4.93, 5.98)	.850	0.13

Table 3. (Continued)

	Baseline (T0)				Δ12 weeks (T2)				
	C		I		C	I	Group differences		
Outcome	*M ± SD*	*N*	*M ± SD*	*N*	*M ± SD*	*M ± SD*	*Δ I - C (95% CI)* [ab]	*P* [ab]	*ES*
Sexual Enjoyment	60.26 ± 24.98	26	45.00 ± 31.11	20	5.13 ± 22.49	10.00 ± 21.90	-0.46 (-12.47, 11.56)	.940	0.22
Future perspective	66.67 ± 25.61	62	60.42 ± 25.11	64	0.54 ± 22.17	5.73 ± 25.58	3.94 (-3.69, 11.57)	.309	0.22
Distressed subgroup									
Distress									
DT	6.46 ± 1.22	24	6.50 ± 1.37	16	-1.67 ± 2.53	-1.19 ± 1.42	0.14 (-1.24, 1.53)	.835	0.23
Problem domains									
Practical	1.14 ± 1.18	28	1.51 ± 1.23	23	-0.35 ± 1.27	-0.66 ± 1.36	0.93 (0.22, 3.94)[c]	.916	
Social	0.83 ± 1.33	27	0.97 ± 1.52	23	-0.02 ± 1.83	-0.61 ± 0.99	2.76 (0.15, 47.20)[c]	.503	
Emotional	1.99 ± 1.43	24	2.80 ± 1.94	22	-0.57 ± 1.51	-1.20 ± 1.78	-0.36 (-1.16, 0.45)	.374	0.38
Spiritual	1.06 ± 1.82	27	1.27 ± 2.21	22	-0.67 ± 1.52	-0.86 ± 1.59	1.08 (0.08, 14.24)[c]	.952	
Physical	2.06 ± 1.18	27	2.21 ± 1.16	22	-1.03 ± 1.01	-1.09 ± 1.26	0.21 (-0.40, 0.44)	.919	0.05
QoL – EORTC-C30									
Global health status/QoL	59.52 ± 19.74	28	58.70 ± 15.78	23	10.42 ± 21.35	10.51 ± 19.50	0.43 (-8.91, 9.76)	.927	0.00
Functional scales									
Physical	69.29 ± 17.90	28	67.25 ± 18.08	23	13.57 ± 15.45	12.46 ± 15.35	-2.05 (-9.09, 4.99)	.561	0.07
Role	54.17 ± 29.62	28	47.83 ± 30.69	23	17.26 ± 26.25	17.39 ± 23.83	-3.38 (-15.45, 8.68)	.575	0.00
Emotional	72.32 ± 19.78	28	67.39 ± 24.22	23	5.56 ± 19.47	10.14 ± 24.87	4.38 (-5.31, 14.06)	.368	0.21
Cognitive	73.81 ± 18.94	28	70.29 ± 25.60	23	8.33 ± 14.70	12.32 ± 22.60	3.28 (-5.88, 12.43)	.475	0.21

Table 3. (Continued)

	Baseline (T0)				Δ12 weeks (T2)				
	C		I		C	I	Group differences		
Outcome	*M ± SD*	*N*	*M ± SD*	*N*	*M ± SD*	*M ± SD*	*Δ I - C (95% CI)*[ab]	*P*[ab]	*ES*
Social	62.50 ± 32.27	28	63.04 ± 21.29	23	17.26 ± 32.55	21.74 ± 20.98	5.03 (-7.20, 17.26)	.412	0.16
QoL – BR23									
Body image	71.91 ± 24.04	27	57.61 ± 26.34	23	6.48 ± 17.19	19.93 ± 27.61	6.65 (-5.22, 18.51)	.265	0.58
Sexual functioning	17.28 ± 21.92	27	18.18 ± 21.15	22	9.26 ± 18.68	9.09 ± 16.04	0.64 (-9.23, 10.51)	.897	0.00
Sexual Enjoyment	62.50 ± 27.82	8	43.33 ± 31.62	10	8.33 ± 29.55	16.67 ± 23.57	-0.75 (-24.85, 23.34)	.948	0.31
Future perspective	58.02 ± 25.47	27	46.38 ± 31.36	23	2.47 ± 22.51	15.94 ± 26.34	11.10 (-2.31, 24.50)	.103	0.55

M=mean; SD=standard deviation; C=control group; I=intervention group; ES=effect size

[a]Complete sample=adjusted for the variable 'receiving current immunotherapy'; [b]Distressed patients=adjusted for the variable 'receiving current radiotherapy'

[c]Logistic regression: Exp(B) and 95% CI for Exp(B) are displayed

DISCUSSION

This study was among the first that evaluated the effects of a web-based tailored psycho-educational intervention for breast cancer patients in the re-entry phase. Although results showed no harmful effects of the ENCOURAGE program, no additional beneficial effects of the program compared to the information leaflets that are part of standard care, were observed. An explanation for the absence of effects may be that certain patients could not further increase in optimism and control over the future. For example, patients who suffer from minor symptoms may not experience an increase herein after use of the program as they feel that their symptoms are already in control. Thus, the program may be effective for a subgroup of patients only. This hypothesis may be reflected by our finding that the program increased feelings of optimism and control over the future more than standard care in the subgroup of patients with clinically elevated distress at baseline. This might imply that distressed patients benefit from such a web-based program. About 30-60% of breast cancer patients suffer from clinically elevated distress during the first 6 months after treatment completion [38]. Similarly, we found 41% of the breast cancer patients to be distressed at baseline of the study. If the program is of help to distressed patients, a relatively large patient population may benefit from the use of the ENCOURAGE program. However, this is a premature conclusion and the results of the subgroup analyses should be interpreted with caution as they were unplanned and underpowered.

Methodological considerations

The absence of findings may, in part, be explained by the design of the program and the intervention onset. Considering the rather low program use, patients may have been exposed too little to the content of the program to solicit any observable effect. The ENCOURAGE program adopted a problem-solving orientation. Problem solving therapy (PST) includes the elements: problem orientation, problem definition, generation of alternatives, decision-making, solution implementation and verification that should be stepwise addressed [18]. Our program incorporated problem orientation and problem definition but the other elements were only implicitly addressed in the psycho-educational material. About 10 sessions are recommended to deliver an effective PST intervention [18,19]. During the 12-week access to the program, patients were not guided throughout all the PST phases, probably contributing to the absence of effects. Future research with the ENCOURAGE program should incorporate all PST phases with homework assignments to practice new skills. The adapted program should be tested

in distressed patients, immediately after completion of chemotherapy to ensure that survivors receive support at an early phase.

Positive adjustment questionnaires, like the CEO questionnaire, are scarce. This questionnaire suited the purposes of the current study: it was specially developed to assess outcomes by the use of web-based programs and was tested in breast cancer patients. However, as baseline scores could not be derived due to its retrospective nature and it is not extensively validated, it might lack sensitivity to measure change.

Several strengths can be noted. The current RCT evaluated a web-based psycho-educational program that targets a gap in survivorship care wherein breast cancer patients report high unmet needs [1,6]. At present, very few of such programs are available. The study was conducted in line with the CONSORT statement for reporting eHealth interventions [39,40]. The included patients varied in socio-demographic and illness-related characteristics and distress reflecting the representativeness of the current sample.

CONCLUSION

In contrast to our expectations, no effects in favor of the ENCOURAGE program were observed. Given the findings that especially distressed patients evaluated the program positively, a subgroup of breast cancer patients might benefit from this intervention. We aim to further develop and test the program. The valuable information of the current study can be used as a starting point for further improvement and use of the program.

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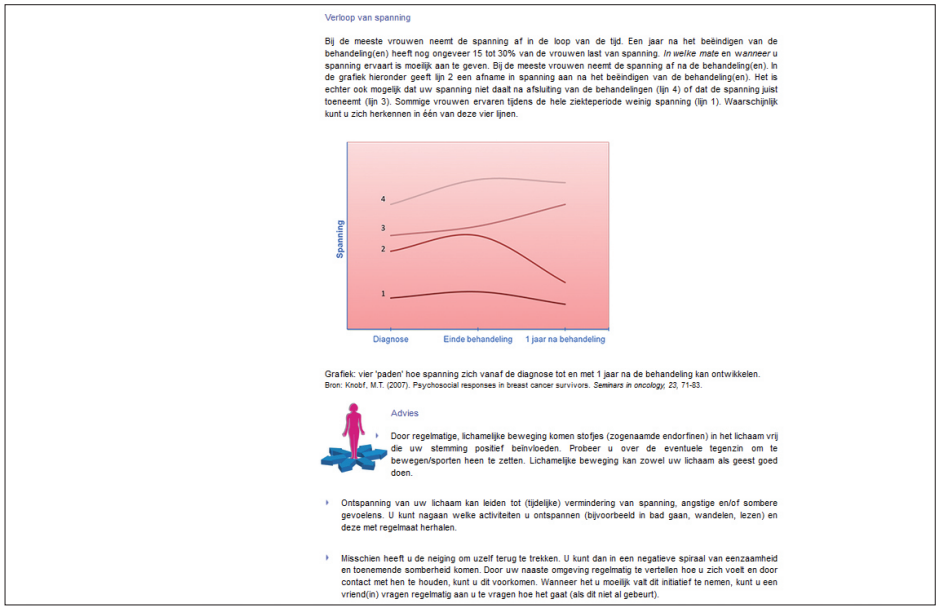
Appendix 1a. Screenshot of the ENCOURAGE program (Dutch): problem identification



Appendix 1b. Screenshot of the ENCOURAGE program (Dutch): psycho-educational material for the problem tension/nervousness (fragment)

CHAPTER 7

Summary and future perspectives

SUMMARY AND FUTURE PERSPECTIVES

Patients confronted with a diagnosis of cancer face numerous challenges in the emotional, social, practical, spiritual and/or physical life domains which may cause psychosocial distress. Appropriate screening and adequate management of patients' distress and underlying problems is of great importance in adjusting well to the cancer experience. Insight into the factors associated with high distress, underlying problems and into the factors related to having a referral wish can aid timely identification and adequate management of patients' distress and problems. However, knowledge is limited regarding these issues.

Web-based programs seem to have potential in supporting patients regarding (self-) management of distress and problems. These programs emerge at a rapid pace [1] but relatively little is known about their effects on the outcomes of patients with cancer [2,3]. A stronger research base is needed to establish the value of these programs for clinical practice.

The main aims of the current thesis were to: 1) increase insight into factors related to high distress, underlying problems and referral wish as measured with the Distress Thermometer (DT) and Problem List (PL) in patients with cancer (part 1) and to; 2) examine effects on patient reported-outcomes, of web-based programs that aim to alleviate psychosocial and physical symptoms (part 2). In this chapter, the results of this thesis are summarized. Also, these results are discussed and suggestions for future research are addressed.

SUMMARY

Chapter 1 introduced the background, aims and outline of the thesis. The concept of distress was described as well as the Dutch guideline on distress management including the Dutch DT/PL (see appendix A for the Dutch and English versions of the DT/PL). Also, current evidence regarding the effects of web-based support programs in patients with cancer was presented.

Part 1 | Distress, underlying problems and referral wish in patients with cancer

In **chapter 2** a first systematic attempt was made to identify optimal DT cutoff scores for patients with different cancer types. A DT cutoff score indicates the minimal score at which patients are perceived as clinically distressed. The aim of the study was to examine the hypothesis that distress levels and cutoff scores depend on cancer type

and/or treatment type. The effect of socio-demographic and illness-related variables on distress was also examined. A large heterogeneous sample of patients with cancer was included (N=1340) varying in socio-demographic and illness-related characteristics including cancer type and varying in distress. Prostate cancer patients reported experiencing lower distress than patients with breast, digestive, lung, gynecologic, head/neck and liver/brain/thyroid cancers. Also, a lower cutoff of ≥4 on the DT was found for prostate cancer patients than the cutoff of ≥5 for breast, digestive, gynecologic and head/neck cancer patients. Lower distress in prostate cancer patients seemed to be partly treatment-related. Two thirds of the prostate cancer patients were in watchful waiting, or underwent surgery or radiotherapy only. These non-intensively treated prostate cancer patients reported lower distress than intensively treated prostate cancer patients, intensively treated non-prostate cancer patients *and* non-intensively treated non-prostate cancer patients. Besides having a non-prostate cancer type, higher distress was associated with receiving treatment that involved more than surgery only and being a younger woman. The DT cutoff scores determined in the current study (either ≥4 or ≥5 depending on cancer type and treatment intensity) can be used as a first screen in screening for clinically elevated distress. As the rule-in ability of the DT is more limited, the identified risk factors i.e. having a non-prostate cancer type, receiving treatment other than surgery only and being a younger woman, may assist in the identification of patients at risk of developing clinically elevated distress. This information can guide clinical decision making of whom to refer to professional psychosocial and/or paramedical health care.

The ultimate goal of distress screening is to refer patients to appropriate health care services, if needed or wished, for treatment of identified problems [4]. However, no conclusive evidence is available on the factors that are related to referral wish. Therefore, in **chapter 3**, we examined effects of cancer patients' perceived distress and problems, socio-demographic and illness-related variables, and social support sufficiency on referral wish. The same large heterogeneous sample was used (see chapter 2). Thirteen percent of the patients requested a referral to psychosocial and/or paramedical health care services, while 21% considered a referral. Independent effects of five variables were found, namely patients who experienced more distress, had more problems in the practical and/or emotional domain, patients who were under active treatment or recently diagnosed, and/or those who were younger were more likely to express a referral wish. Distress level and emotional and practical problems appeared to be more powerful predictors of referral wish than the socio-demographic, social and clinical characteristics. This has not been reported before and suggests that responses

on the DT/PL provide more information to health care professionals when deciding on whom to refer than just socio-demographic, social and clinical characteristics. Patients with a high distress score (DT≥5) were three times more likely to express a referral wish than patients with a low score (DT<5). However, not all with a distress score of ≥5 on the DT expressed a referral wish and some patients with low distress desired a referral. This was also reflected by the finding that variables predicting higher distress (**chapter 2**) were not identical to the variables associated with a referral wish (**chapter 3**). For example, patients with prostate cancer reported lower levels of distress than patients with other types of cancer whereas the percentage of patients with prostate cancer expressing a referral wish was similar to that of patients with a non-prostate cancer type. These results suggest that screening for distress is helpful in identifying patients with a high symptom burden but is insufficient to determine who would desire or need additional care, even when used in combination with the risk variables identified in chapter 2. This underlines the importance of discussing DT/PL responses including distress level, distress-underlying problems and referral wish with all patients, regardless of their distress level.

In **chapter 4**, distress levels, underlying problems, referral wish and supportive health care use were examined in a cross-sectional group of breast cancer survivors at two-time points with a one-year time interval. The survivors had completed chemotherapy 1 to 5 years earlier. Also, socio-demographic and illness-related variables and underlying problems associated with continuing elevated distress were explored. Continuing elevated distress was defined as a distress (DT) score of ≥5, at both assessment points. At least one-third of the longer-term survivors experienced clinically elevated distress at one of the time points (DT≥5), and one in four survivors reported clinically elevated distress at both time points. A shorter time since diagnosis, more health care use, and a higher level of practical, social, emotional and physical problems were significantly associated with continuing elevated distress. Physical problems were most strongly related to continuing elevated distress. Fatigue and lack of physical fitness were most frequently reported by survivors in this setting. A large proportion of survivors was or had been using supportive health care services, mostly from a psychologist and/or a physical or lymphedema therapist. Eleven percent of the survivors wished a referral and 37% considered a referral. At the assessment one year later, 16% wished and 17% considered a referral. These results indicate that screening and management of distress, problems and referral wish are important, even years after chemotherapy completion as a substantial proportion of breast cancer survivors continue to report elevated distress and problems. Special attention should be paid to survivors reporting

physical problems, especially fatigue and lack of physical fitness, since these problems seem to be most strongly related to continuing elevated distress.

Part 2 | Web–based support programs for patients with cancer

Many patients with cancer turn to the internet to search for cancer-related information. Already in 2007, a Dutch cross-sectional survey on cancer-related internet use demonstrated that 60% of patients themselves frequently used the internet and 9% asked others to search for them [5]. Internet-based support programs seem particularly well-suited to fulfill unmet supportive care needs and can aid patients in self-managing psychosocial and physical symptoms experienced [6]. Generally, patients with cancer have a positive attitude towards self-management and web-based interventions. Patients are especially interested in web-based programs that provide support on how to handle and/or cope with the consequences of cancer [7]. The second part of this thesis examined the effects of web-based support programs on patient reported outcomes. In order to increase the existing knowledge on the effects of web-based support programs, a systematic literature analysis was performed in **chapter 5.** More specifically, it was examined whether these programs alleviate psychosocial and/or physical symptoms resulting from cancer diagnosis and treatment. Database and citation searches resulted in the selection of 16 eligible studies. Results showed that the majority of the included studies (9 of 16 studies) reported positive effects, especially on fatigue, social support and distress. The review was the first to link effectiveness to program type. The effectiveness varied across program type. All web-based programs that integrated multiple services such as information, support, communication and/or coaching services reported at least one significant positive effect, mainly on social support and quality of life. Only one of the included studies on web-based social support groups in which patients share personal experiences, feelings and information regarding psychosocial and/or physical symptoms, reported a positive effect. This was also the case for studies on web-based therapy, in which face-to-face therapy for specific symptoms (e.g. sexual problems, depressive symptoms) was replaced by web-based communication. The methodological quality assessment in our review showed that many studies on web-based support programs need improvement regarding study design and/or report of the study. Also, the included studies made use of many different outcomes. These methodological issues and heterogeneity hamper firm conclusions about the effectiveness of web-based programs on symptom management. In short, the results are promising but more studies are needed using rigorous study designs and standards in reporting before these programs will be integrated in routine cancer care.

In **chapter 6** a multicenter randomized controlled trial that was performed to examine the effects of the ENCOURAGE program is described**.** The ENCOURAGE program is a web-based tailored psycho-educational program for breast cancer patients in the re-entry phase (i.e. the first year after primary treatment completion) which aims to empower patients to take control over prevailing problems and to adjust to life after treatment. Several self-reported outcomes were assessed to test the effect of the program including the primary outcome 'optimism and feelings of control over the future'. Of the patients, 71% (completely) agreed with having a positive attitude towards the program. In contrast to our expectations, no effects in favor of the ENCOURAGE program were observed compared to the information leaflets that are standardly given to all patients. However, the program showed a positive effect on the primary outcome in *distressed* patients (DT score ≥5) in the intervention group compared to distressed patients in the control group. The effect size was medium to large (Cohen's *d*=0.65) indicating a relevant difference. Also, 81% of distressed patients (completely) agreed with having a positive attitude towards the program. Thus, the program may be effective for distressed patients only but this hypothesis needs further testing as the subgroup analyses were underpowered. The absence of findings for the complete group may also be explained by the design of the program and the intervention onset. The ENCOURAGE program adopted a problem-solving orientation: some elements of the problem solving therapy (PST) were only implicitly addressed in the psycho-educational material. Thus, during the 12-week access to the program, patients were not guided throughout all the PST phases, possibly contributing to the absence of effects. Future research with the ENCOURAGE program should incorporate all PST phases with homework assignments to practice new skills. The adapted program should be tested in distressed patients, immediately after completion of chemotherapy to ensure that survivors receive support at an early phase. Concluding, the results of the ENCOURAGE study are promising as distressed patients evaluated ENCOURAGE positively and seem to benefit from the intervention. The issues raised regarding patient selection and use of an intervention which is firmly based on a theoretical model, can be used as a starting point for further improvement and use of the program.

DISCUSSION AND FUTURE PERSPECTIVES

Part 1 | Distress, underlying problems and referral wish in patients with cancer

The value of distress screening in clinical practice

During the last years a strong case is being made to routinely screen for distress in oncologic practice as clinicians may overlook the need of supportive care [8]. A substantial number of patients report high distress but no referral wish and some patients with low distress desire a referral (chapter 3). The question may come to mind whether screening for distress and underlying problems should be discarded and replaced by a direct question to patients whether patients have a need for additional supportive health care [9,10]. It is important to ask patients about the presence of a referral wish as this may empower patients to make their own choices [11]. However, replacing the distress screening process by a simple help question would provide insufficient information. If distress level and referral wish do not align, this is valuable information which can guide the discussion of DT/PL responses. Chapter 3 provides an in-depth discussion of the possible reasons why patients with clinically elevated distress may not wish a referral. Motives to decline a referral vary substantially. Communication between a health care provider and a patient may uncover patient's motive(s), possibly leading to referral and uptake of professional care. Similarly, patients with overall low distress may desire a referral to manage a problem they experience. Discussion of the DT/PL response with patients who report low distress can provide important insight into the severity of separate problems and can guide subsequent referral practice. Thus, optimally supporting patients will be achieved best by screening and discussing distress level, distress-underlying problems and referral wish.

Future directions for distress screening research

As the psychometric properties of the DT/PL and the effectiveness of distress screening become increasingly established [12,13], a shift in research focus is required. During the last years, considerable progress has been made in integrating distress screening into routine cancer care, worldwide and in the Netherlands [14]. Still many organizations do not use a distress screening program. As implementation of a distress screening program requires more than simply use of a screening tool, organizations that wish to implement such programs are faced with several practical implementation issues [15]. Criteria that can aid in implementation of a distress screening program have been defined, such as appointing a project manager and setting goals which are frequently

evaluated, but evidence based on rigorous studies is lacking [4]. Also, barriers and facilitators for successful implementation require further investigation.

Acceptability of the screening procedure to patients has been perceived as a key factor in successful implementation [13,16]. A recent article found that patients who received information about the purpose of the screening procedure and the DT/PL and who were informed about availability and expertise of allied/psychosocial care professionals, expressed a more favorable opinion regarding screening and DT/PL completion. Also, patients appreciated discussion of DT/PL responses with a health care professional and this was related to recommending the screening procedure to others [17]. Future research may identify additional factors that are related to the acceptability and effectiveness of different screening procedures and may examine whether preferences vary across patients.

Acceptability of the procedure to health care professionals' is a second factor. Health care professionals may perceive that screening takes valuable time from their regular tasks [15]. Research indicated that this concern is unfounded. In fact, time is used more efficiently as only problems that are reported by the patient are discussed [4,18,19]. Acceptability can be enhanced by informing health care professionals about efficient use of time. Health care professionals may also be reluctant about screening as their screening and communication skills are limited. Targeted training can improve these skills [20]. An important aspect herein is training regarding referral pathways and communicating with patients about a referral. Screening showed to be more effective when linked to triage, predetermined pathways for referral, and/or an intervention [21-23]. Future research may focus on the content and extensiveness of such referral instructions health care professionals need to optimally support patients.

Due to screening, more patients may be referred to additional health care. As a consequence, costs of health care use may increase. Stepped-care may be a useful approach as it is regarded as efficient in terms of costs and use of resources. Stepped-care provides patients in need with a least resource-intensive treatment but is followed, if necessary, by more resource-intensive treatments [24]. A low-resource intensive intervention is for example a web-based intervention or a guided self-help intervention while use of a specialized psychosocial health care professional [e.g. psychologist, psychiatrist] is highly resource intensive. Recent studies showed that stepped-care improved patients with cancer' well-being [25] and referral practice [26]. The subsequent steps varied across studies and the question what steps are most effective can be the target of future research. Also, studies on the cost-effectiveness of the stepped-care approach are scarce and need further study [27].

Part 2 | Web–based support programs for patients with cancer

Future research into the effects of web-based programs

As current research on web-based programs for patients with cancer is heterogeneous in terms of measured outcomes, quality and report of the studies, it is difficult to formulate best-practice recommendations [28,29]. The use of standards to which studies should comply, can enhance the scientific value of research in this area. Special papers were published on the relevance of the Consolidated Standards of Reporting Trials (CONSORT) statement for eHealth[2] research including an adapted checklist for research in this area [31,32]. Applying these standards both improve reporting of eHealth research and may also serve as a guide for researchers in design of their interventions and studies [31]. Additionally, use of these standards can enhance homogeneity of the studies.

As it is expected that routine care and the use of web-based interventions will be increasingly intertwined in the future, the need for rigorous methods to evaluate eHealth interventions is of great importance [30,33]. Randomized controlled trials (RCTs) have been perceived as the 'gold standard' in examining the efficacy of therapeutic interventions but may have some disadvantages with respect to eHealth interventions research [1,34]. For example, randomizing patients between a control and intervention condition may be unethical when it is strongly expected that the web-based intervention is superior to the control condition i.e. violation of the equipoise principle [34,35]. A stepped wedge cluster design may be a solution to this problem. In this design, clusters, for example hospitals, are randomly allocated to the intervention or the control condition. Initially, all clusters are in the control condition. The intervention is being implemented sequentially. Eventually, all clusters will be receiving the intervention[35, 36]. Another advantage of this design is that the intervention is evaluated *during* implementation in routine practice thus, speeding up the availability of the intervention [37]. This is important advantage as the classical RCT is time-consuming while eHealth interventions develop in a rapid pace. Another way to increase the efficiency of eHealth research is to conduct small sample studies that examine sub-questions regarding intervention effectiveness. Third, the use of factorial designs allows for simultaneous evaluation of multiple intervention components with no loss of power compared to a classical RCT in which only one intervention type/component can be examined [1].

2 " 'eHealth' generally refers to the use of information technology, including the Internet, digital gaming, virtual reality, and robotics, in the promotion, prevention, treatment, and maintenance of health."; as defined by Borelli & Ritterband, 2015 (30).

Finally, in eHealth effectiveness research, it is important to develop theoretical models that capture the mechanisms underlying an intervention [1,38,39]. At present, the large majority of the studies on web-based interventions make too little use a of a theoretical model in the development of the intervention and in the identification of outcome measures [39]. Mediation and moderation analyses are helpful in building these models. Mediation analyses provide insight in how interventions work i.e. these analyses can examine if the theory of the intervention is correct. Moderation analyses identify factors that enhance or decrease the effectiveness of an intervention. For example, an intervention may be more effective for younger than for older patients with cancer and/or for certain cancer subpopulations. Such information is important as it aids in optimizing the intervention.

Clinical implications

The use of eHealth can be of great value in clinical practice given its cost-efficiency and wide accessibility. In the Netherlands, the popularity of eHealth increased during the last years. In 2014, mental health organizations reported that 50% of their patients will be treated using eHealth soon [40]. National mental health associations have adopted the implementation of eMental health as a key policy theme. A popular approach in mental health care is blended care: a combination of online and face-to-face therapy. It is expected that blended care combines the advantages of face-to-face and online treatment. Research into the safety, efficacy and efficiency of blended treatment has only recently begun [37]. Recent trials reported promising results [41,42], including for cancer patients [43] but these studies need replication in rigorous study designs. Also, a rationale for the development of blended care is often lacking and general principles i.e. what type of 'blend' works for whom, and why is unclear at present [44]. Thus, while eHealth can enrich health care, it is important that implemented web-based interventions are based on evidence. As suggested in the previous paragraph, scientific evaluation of these interventions can both be rigorous and fast.

Another challenge is the availability of eHealth interventions. Patient preferences with respect to eHealth vary considerably [45]. It cannot be expected that a few accessible interventions will cover the supportive care needs of all patients. We recommend that more effort should be put in the disclosure of available evidence-based eHealth interventions. For example, a portal website could be constructed which contains all available eHealth interventions including websites, apps and social media for patients with cancer. As such, patients can choose what type of intervention matches their needs and preferences.

CONCLUSION

Appropriate screening and adequate management of patients' distress and underlying problems is of great importance in adjusting well to the cancer experience. The current thesis showed different approaches by which patients can be supported in dealing with distress and problems. Distress screening is a key aspect in the support of patients. Knowledge of factors related to high distress, underlying problems and referral wish (which was identified), can aid in the optimal use of the DT/PL by health care professionals and hence, in adequately referring patients who are in need of additional support for their problems. The current thesis also showed that web-based support programs are feasible and can be effective in alleviating patients' problems. In the coming years, it is expected that the evidence for the efficacy of web-based interventions will further accumulate. Thus, both screening and web-based programs can be of valuable addition to traditional practices in cancer care. Hopefully, these approaches will soon be fully integrated in routine cancer care worldwide.

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Nederlandse samenvatting

NEDERLANDSE SAMENVATTING

De diagnose ‘kanker’ en de daaropvolgende behandeling(en) hebben ingrijpende gevolgen voor de patiënt en zijn/haar naasten. Als gevolg hiervan kunnen problemen ontstaan op lichamelijk gebied maar ook op emotioneel, sociaal, praktisch en/of levensbeschouwelijk/spiritueel gebied. Het totaal van deze problemen wordt aangeduid met de term ‘distress’ (‘last’). Psychosociale signalering - het proces van het detecteren van de aard en ernst van problemen van patiënten, communicatie over deze problemen en eventuele doorverwijzing - is belangrijk om distress op het spoor te komen en om als zorgverlener de patiënt hierin adequaat te kunnen ondersteunen. Inzicht in de factoren die samenhangen met het ervaren van veel distress, met onderliggende problemen en met het hebben van een verwijswens kan bijdragen aan het tijdig herkennen van patiënten met veel distress en problemen, en vroegtijdige doorverwijzing naar een psychosociale en/of paramedische zorgverlener realiseren.

Online interventies worden in toenemende mate gebruikt in de gezondheidszorg. Ook voor patiënten met kanker komen steeds meer online programma’s beschikbaar. Sommige van deze programma’s ondersteunen patiënten in het omgaan met psychosociale en/of lichamelijke klachten die het gevolg zijn van de ziekte en de behandeling(en). De wetenschappelijke onderbouwing van deze (zelf)hulpprogramma’s is echter nog mager. Meer bewijsvoering is dus noodzakelijk om de waarde hiervan voor patiënten met kanker te kunnen vaststellen.

Het doel van dit proefschrift was tweeledig: 1) om inzicht te verkrijgen in de factoren die samenhangen met het ervaren van veel distress en problemen en in het hebben van een verwijswens naar psychosociale en/of paramedische zorg bij patiënten met kanker; 2) onderzoeken wat de effecten op patiënt-gerapporteerde uitkomsten zijn van online (zelf)hulpprogramma’s die als doel hebben om patiënten te ondersteunen in het omgaan met psychosociale en/of lichamelijke problemen.

In **hoofdstuk 1** zijn de achtergrond, de doelen, en de opbouw van het proefschrift beschreven. Het concept distress wordt besproken evenals de Nederlandse richtlijn ‘Detecteren behoefte psychosociale zorg’. Tevens wordt de ‘Distress Thermometer and Problem List’ (DT/PL) geïntroduceerd, in het Nederlands de ‘Lastmeter’ genoemd (zie appendix A voor de Engelse en de Nederlandse versie). De Lastmeter is een vragenlijst voor patiënten waarmee de zorgverlener zicht kan krijgen op de aard en ernst van de problemen die de patiënt ervaart (distress). Ook kan de patiënt op de Lastmeter aan-

geven of hij/zij wenst om met een zorgverlener over de ervaren problemen te praten en eventueel, met wie hij/zij wil praten.

In hoofdstuk 1 wordt tevens de huidige kennis uiteengezet over de effecten van online (zelf)hulpprogramma's voor patiënten met kanker. Online programma's die zich richten op het verlichten van psychosociale en/of lichamelijke problemen van patiënten hebben in dit proefschrift de aandacht. De aanwezige kennislacunes met betrekking tot deze programma's worden toegelicht.

Deel 1 | Distress, onderliggende problemen en een verwijswens bij patiënten met kanker

In **hoofdstuk 2** zijn de optimale DT-afkapwaardes voor patiënten met verschillende soorten kanker onderzocht. Op basis van de afkapscore kunnen patiënten opgespoord worden met klinisch verhoogde distress (case). Het doel van de studie was het onderzoeken van de hypothese dat distress en de afkapwaarde afhankelijk zijn van het soort kanker en/of van het type behandeling. De effecten van sociaal-demografische en andere ziekte-gerelateerde variabelen op distress werden ook onderzocht. Een grote heterogene groep van patiënten met kanker werd geïncludeerd (N=1340), variërend in sociaal-demografische en ziekte-gerelateerde kenmerken. De resultaten wezen uit dat patiënten met prostaatkanker minder distress rapporteren dan patiënten met borst-, spijsverterings-, long-, gynaecologische, hoofd/hals- en lever/hersenen/schildklierkanker. Ook werd een lagere afkapwaarde van ≥4 op de DT gevonden bij patiënten met prostaatkanker in vergelijking met de afkapwaarde van ≥5 voor borst-, spijsverterings-, gynaecologische en hoofd/hals-kankerpatiënten. Lagere distress bij patiënten met prostaatkanker leek deels gerelateerd aan de behandeling. Twee-derde van de prostaatkankerpatiënten hadden (nog) geen behandeling ontvangen maar bij hen werd het verloop van de ziekte afgewacht (ook wel "watchful waiting" genoemd) of patiënten ondergingen alleen een operatie of radiotherapie. Deze niet-intensief behandelde prostaatkankerpatiënten rapporteerden minder distress dan intensief behandelde prostaatkankerpatiënten (een behandeling die meer behelsde dan alleen een operatie of radiotherapie of "watchful waiting") en dan intensief behandelde niet-prostaatkankerpatiënten (een behandeling die meer inhield dan alleen een operatie). Opvallend is dat niet-intensief behandelde prostaatkankerpatiënten ook minder distress rapporteerden dan niet-intensief behandelde niet-prostaatkankerpatiënten. Naast het hebben van een soort van kanker anders dan prostaatkanker, was een hogere distress score gerelateerd aan een behandeling die meer inhield dan alleen een operatie en jongere vrouwen bleken meer risico te lopen op hogere distress dan oudere vrouwen

en dan mannen. De DT-afkapwaardes die in het huidige onderzoek zijn bepaald (≥4 of ≥5, afhankelijk van het soort van kanker en de intensiteit van de behandeling) kunnen worden gebruikt als een eerste screening op de aanwezigheid van klinisch verhoogde distress. Aangezien de sensitiviteit en specificiteit van de DT niet 100% zijn, kunnen de geïdentificeerde risicofactoren (een soort van kanker anders dan prostaatkanker, een intensievere behandeling dan alleen een operatie en het zijn van een jongere vrouw) verder helpen bij de identificatie van patiënten die het risico lopen op klinisch verhoogde distress. Deze informatie kan als leidraad dienen in de klinische besluitvorming welke patiënten te verwijzen naar psychosociale en/of paramedische zorg.

Het uiteindelijke doel van distress screening is om patiënten door te verwijzen naar passende psychosociale en/of paramedische zorg, indien nodig of gewenst, voor de behandeling van geïdentificeerde problemen. Er is echter geen sluitend bewijs voorhanden met betrekking tot de factoren die gerelateerd zijn aan het hebben van een verwijswens. Daarom is in **hoofdstuk 3** gekeken naar de effecten van distress en problemen, sociaal-demografische en ziekte-gerelateerde variabelen en de sociale steun die patiënten ervaren op de verwijswens. Dezelfde grote heterogene groep patiënten als in **hoofdstuk 2** is daarvoor gebruikt. Dertien procent van de patiënten wenste een verwijzing naar psychosociale en/of paramedische zorg, terwijl 21% een verwijzing overwoog. Voor vijf variabelen werd een onafhankelijk effect gevonden op het hebben van een verwijswens: patiënten die meer distress rapporteerden en/of meer problemen in het praktische of emotionele domein, die ten tijde van het onderzoek een medische behandeling ondergingen (gerelateerd aan kanker) of recent waren gediagnosticeerd, en patiënten die jonger waren, hadden vaker een wens om doorverwezen te worden. De mate van distress en de aanwezigheid van emotionele en praktische problemen leken betere voorspellers van een verwijswens dan sociaal-demografisch en ziekte-gerelateerde kenmerken en sociale steun. Dit is nog niet eerder aangetoond en suggereert dat de antwoorden op de Lastmeter bruikbaardere informatie verstrekken aan zorgverleners bij het nemen van beslissingen over wie te verwijzen dan alleen sociaal-demografische en ziekte-gerelateerde kenmerken en sociale steun. Patiënten met klinisch verhoogde distress (DT≥5) hadden een drie keer zo grote kans om een verwijswens te rapporteren dan patiënten met een score onder het afkappunt (DT<5). Echter, niet alle patiënten met klinisch verhoogde distress uitten een verwijswens en sommige patiënten met lage distress wensten een verwijzing. Dit kwam ook naar voren uit de bevinding dat variabelen die samenhangen met een hogere distress score (**hoofdstuk 2**) niet identiek zijn aan de variabelen die samenhangen met een verwijswens (**hoofdstuk 3**). Patiënten met prostaatkanker rapporteerden bijvoorbeeld mind-

er distress dan patiënten met andere soorten kanker, terwijl het percentage patiënten met prostaatkanker dat een verwijzing wenste vergelijkbaar was met dat van patiënten met een niet-prostaat soort van kanker. Deze resultaten suggereren dat screening van distress behulpzaam is bij het identificeren van patiënten met een hoge symptoomlast, maar onvoldoende is om te bepalen wie extra zorg zou willen of nodig heeft, zelfs wanneer het wordt gebruikt in combinatie met de risicovariabelen die in **hoofdstuk 3** werden geïdentificeerd. Dit onderstreept het belang van het bespreken van de antwoorden op de Lastmeter inclusief de mate van distress, problemen en de verwijswens met alle patiënten, ongeacht of hun distress score boven of onder het afkappunt ligt. Dit proces is van cruciaal belang om adequaat te kunnen beslissen welke patiënten een verwijzing nodig hebben en naar welk type zorgverlener.

In **hoofdstuk 4** zijn distress, onderliggende problemen, verwijswens en gebruik van psychosociale en paramedische zorg onderzocht in een cross-sectionele groep van overlevenden van borstkanker. De variabelen zijn gemeten op twee tijdstippen met een tijdsinterval van één jaar. De overlevenden hadden tussen één tot vijf jaar geleden een behandeling met chemotherapie afgerond. Ook is onderzocht welke sociaal-demografische en ziekte-gerelateerde variabelen en welke problemen gerelateerd zijn aan aanhoudende verhoogde distress. Aanhoudende verhoogde distress werd gedefinieerd als een distress (DT) score van 5 of hoger gemeten op beide tijdstippen. Tenminste 1/3 van de overlevenden ervoer klinisch verhoogde distress op één van de tijdstippen (DT≥5), en één op de vier overlevenden rapporteerde klinisch verhoogde distress op beide tijdstippen. Een kortere tijd sinds diagnose, een hogere mate van zorggebruik, en meer praktische, sociale, emotionele en/of lichamelijke problemen vergrootte de kans dat overlevenden aanhoudende verhoogde distress rapporteerden. Lichamelijke problemen waren het sterkst gerelateerd aan aanhoudende verhoogde distress. Vermoeidheid en gebrek aan conditie werden het vaakst als probleem genoemd door overlevenden. Een groot deel van de overlevenden heeft of had ondersteunende gezondheidszorg ontvangen, meestal van een psycholoog en/of een fysio-/lymfoedeemtherapeut. Elf procent van de overlevenden wenste een verwijzing en 37% overwoog een verwijzing. Bij de beoordeling één jaar later, wenste 16% een verwijzing en overwoog 17% een verwijzing. Deze resultaten wijzen erop dat het opsporen en behandelen van distress belangrijk zijn, ook jaren nadat de behandeling met chemotherapie is afgerond. Aandacht van zorgverleners voor lichamelijke problemen, vooral voor vermoeidheid en gebrek aan conditie, is extra belangrijk omdat deze problemen het sterkst samenhangen met aanhoudende verhoogde distress.

Deel 2 | Online programma's voor patiënten met kanker

Veel patiënten met kanker wenden zich tot het internet om te zoeken naar informatie over hun ziekte. Reeds in 2007 toonde een Nederlands cross-sectioneel onderzoek over kanker-gerelateerd internetgebruik aan dat 60% van de patiënten vaak het internet doorzocht en 9% van de patiënten vroeg anderen om naar informatie te zoeken. Online (zelf)hulpprogramma's lijken bijzonder geschikt om ondersteunende zorg te verlenen en kunnen patiënten bovendien helpen bij zelfmanagement van psychosociale en lichamelijke symptomen. Over het algemeen hebben patiënten met kanker een positieve houding ten opzichte van zelfmanagement aan de hand van online (zelf)hulp.

In het tweede deel van dit proefschrift onderzochten we de effecten van online (zelf)hulpprogramma's op patiënt-gerapporteerde uitkomsten. Om de bestaande kennis over de effecten van online (zelf)hulpprogramma's te vergroten, werd systematisch literatuuronderzoek uitgevoerd in **hoofdstuk 5**. Aan de hand van deze literatuuranalyse werd nagegaan of deze programma's psychosociale en/of lichamelijke symptomen, als gevolg van de diagnose en de behandeling van kanker, kunnen verlichten. Zoekopdrachten in databases en referentielijsten resulteerden in de selectie van 16 studies die voldeden aan onze criteria. De resultaten toonden aan dat de meerderheid van de geïncludeerde studies (9 van 16 studies) positieve effecten rapporteerden, vooral op uitkomsten als vermoeidheid, ervaren sociale steun en angst. De literatuuranalyse deed ook een eerste poging om de effectiviteit van de online (zelf)hulpprogramma's te koppelen aan de inhoud van de programma's. De effectiviteit varieerde tussen de verschillende typen programma's. Alle studies waarin programma's werden onderzocht die meerdere functionaliteiten bevatten zoals informatie/psycho-educatie, mogelijkheden voor communicatie met een zorgverlener en/of coaching services, rapporteerden minstens één significant positief effect, voornamelijk op sociale steun en kwaliteit van leven. Echter, slechts één van de geïncludeerde studies waarin patiënten op internetfora onderling contact hadden over psychosociale en/of lichamelijke symptomen die zij ervaarden, liet een positief effect zien. Dit was ook het geval voor studies waarin face-to-face therapie voor specifieke symptomen (bijvoorbeeld seksuele problemen, depressieve symptomen) werd vervangen door online communicatie.

De methodologische kwaliteitsbeoordeling toonde aan dat veel studies over online (zelf)hulpprogramma's verbetering behoeven met betrekking tot de studie opzet en/of de wijze van rapporteren over het onderzoek. Ook maakten de geïncludeerde studies gebruik van veel verschillende uitkomstmaten. Door deze methodologische zwakheden en heterogeniteit in uitkomstmaten is het lastig om heldere conclusies te kunnen trekken over de effectiviteit van online (zelf)hulpprogramma's. Meer onderzoek is nodig

waarbij kwalitatief hoogstaande studiemethoden en rapportagestandaarden worden gebruikt (zoals de 'Consolidated Standards of Reporting Trials (CONSORT)-statement for eHealth') voordat een definitieve(re) conclusie kan worden getrokken.

Hoofdstuk 6 beschrijft een gerandomiseerde studie waarin werd onderzocht wat de effecten zijn van het online 'ENCOURAGE-programma'. Patiënten met borstkanker afkomstig uit twee verschillende ziekenhuizen werden at random in de interventiegroep geplaatst (ENCOURAGE-programma) of in de controlegroep. Het ENCOURAGE-programma is een online programma waarin psycho-educatie op maat wordt gegeven aan patiënten met borstkanker die hun primaire behandeling minder dan een jaar geleden hebben afgerond. Het doel van het programma is om patiënten te helpen in het omgaan met eventuele psychosociale en/of lichamelijke gevolgen van de diagnose en behandeling(en) en uiteindelijk om hun leven weer op te kunnen pakken. Verschillende patiënt-gerapporteerde uitkomsten werden gebruikt om het effect van het programma te testen, inclusief de primaire uitkomstmaat 'optimisme en gevoelens van controle over de toekomst'. Van de patiënten was 71% het (volledig) eens met de stelling dat hij/zij positief tegenover het programma stond. In tegenstelling tot onze verwachtingen werden geen effecten ten gunste van het ENCOURAGE-programma gevonden wanneer de interventiegroep werd vergeleken met de controlegroep. In de controlegroep ontvingen patiënten standaardzorg. In zowel de interventie- als de controlegroep ontvingen patiënten een informatiebrochure over borstkanker en een brochure over psychosociale aspecten van kanker. Nadere subgroep analyses wezen uit dat het ENCOURAGE-programma wel een positief effect had op de primaire uitkomstmaat voor patiënten met klinisch verhoogde distress (DT score ≥5) in de interventiegroep in vergelijking met patiënten met verhoogde distress in de controlegroep. De effectgrootte was gemiddeld tot groot (Cohen's d = 0.65), hetgeen een relevant verschil aangeeft. Ook gaf 81% van de patiënten met verhoogde distress aan dat zij het (volledig) eens waren met de stelling dat hij/zij positief tegenover het programma stond. Het programma is dus mogelijk effectief voor patiënten met klinisch verhoogde distress. Deze hypothese moet echter nog verder worden getest omdat het aantal patiënten waarover de analyses zijn gedaan klein was.

De afwezigheid van positieve resultaten voor de totale groep kan mogelijk ook worden verklaard door het ontwerp van het programma en/of door het tijdstip waarop patiënten startten met het gebruik ervan. Het ENCOURAGE-programma maakt gebruik van een probleemoplossende oriëntatie. Echter, in het programma werd niet gebruik gemaakt van alle vijf fases van de probleemoplossende therapie (PST): hoewel probleemoriëntatie en probleemdefinitie aan bod kwamen werden de andere fases

(bedenken van oplossingen, kiezen van een oplossing en implementatie en evaluatie van de oplossing) alleen impliciet behandeld in het psycho-educatieve materiaal. Tijdens de 12 weken dat patiënten toegang hadden tot het programma werden zij dus niet door alle PST fasen geleid, wat mogelijk heeft bijgedragen aan de afwezigheid van effecten. Het is dan ook aan te raden om alle PST fasen in het ENCOURAGE-programma te incorporeren inclusief huiswerkopdrachten om nieuw verworven vaardigheden te oefenen. Het aangepaste programma kan het beste getest worden bij patiënten met klinisch verhoogde distress, onmiddellijk na voltooiing van chemotherapie om ervoor te zorgen dat patiënten in een vroege fase ondersteuning krijgen. Concluderend, de resultaten van de ENCOURAGE-studie zijn veelbelovend, omdat patiënten die veel distress rapporteerden ENCOURAGE positief beoordeelden en lijken te profiteren van de interventie. De bovengenoemde kwesties kunnen als startpunt worden gebruikt voor verdere verbetering en gebruik van het programma.

CONCLUSIE

Aandacht voor de mate van distress en van de aard van onderliggende problemen is van groot belang voor patiënten met kanker om het leven weer op te kunnen pakken na de diagnose en de behandeling(en). Psychosociale signalering vormt een belangrijk element in het ondersteunen van patiënten. Kennis van factoren die samenhangen met veel distress, problemen en het hebben van een verwijswens (welke in dit proefschrift zijn geïdentificeerd), kan helpen bij een optimaal gebruik van de Lastmeter door zorgverleners en daarmee in het adequaat verwijzen van patiënten die behoefte hebben aan extra professionele hulp voor hun problemen. Dit proefschrift toonde ook aan dat online (zelf)hulpprogramma's haalbaar en effectief kunnen zijn in het verlichten van problemen van patiënten. Het is de verwachting dat het bewijs voor de effectiviteit van online (zelf)hulpprogramma's de komende jaren verder zal toenemen. Zowel het proces van psychosociale signalering als het gebruik van online (zelf)hulpprogramma's kunnen een waardevolle aanvulling zijn op de traditionele zorg voor patiënten met kanker. Hopelijk zullen deze methoden binnenkort wereldwijd volledig onderdeel zijn van de dagelijkse zorg voor patiënten met kanker.

Appendix A

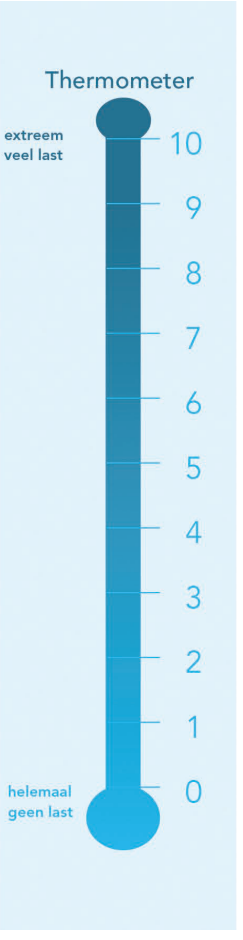
Dutch and English versions of the DT/PL

lastmeter

Invuldatum:

..... - ..... - .....
(dag - maand - jaar)

Vul eerst de thermometer in:
Omcirkel het nummer op de thermometer dat het best samenvat hoeveel last u de afgelopen week (inclusief vandaag) hebt gehad op lichamelijk, emotioneel, sociaal en praktisch gebied.



Probleemlijst

Wilt u voor onderstaande gebieden aangeven of u de afgelopen week (inclusief vandaag) hier moeite mee hebt gehad of problemen bij hebt ervaren. Wilt u elke vraag beantwoorden?

Als u Ja hebt geantwoord, wilt u dan met een cijfer van 1-10 aangeven hoeveel moeite of problemen u hebt ervaren? (1 = nauwelijks moeite of problemen en 10 = extreem veel moeite of problemen).

ja	indien ja, hoeveel	nee	**Praktische problemen**
○	.....	○	zorg voor kinderen
○	.....	○	wonen / huisvesting
○	.....	○	huishouden
○	.....	○	vervoer
○	.....	○	werk / school / studie
○	.....	○	financiën
○	.....	○	verzekering

ja		nee	**Gezins- / sociale problemen**
○	.....	○	omgang met partner
○	.....	○	omgang met kinderen
○	.....	○	omgang met familie / vrienden

ja		nee	**Emotionele problemen**
○	.....	○	greep hebben op emoties
○	.....	○	herinneren van dingen
○	.....	○	zelfvertrouwen
○	.....	○	angsten
○	.....	○	neerslachtigheid / somberheid
○	.....	○	spanning
○	.....	○	eenzaamheid
○	.....	○	concentratie
○	.....	○	schuldgevoel
○	.....	○	controleverlies

ja		nee	**Religieuze/spirituele problemen**
○	.....	○	zin van het leven / levensbeschouwing
○	.....	○	vertrouwen in God / geloof

ja	indien ja, hoeveel	nee	**Lichamelijke problemen**
○	.....	○	uiterlijk
○	.....	○	veranderde urine – uitscheiding
○	.....	○	verstopping / obstipatie
○	.....	○	diarree
○	.....	○	eten
○	.....	○	opgezwollen gevoel
○	.....	○	koorts
○	.....	○	mondslijmvlies
○	.....	○	misselijkheid
○	.....	○	droge, verstopte neus
○	.....	○	pijn
○	.....	○	seksualiteit
○	.....	○	droge, jeukerige huid
○	.....	○	slaap
○	.....	○	benauwdheid
○	.....	○	duizeligheid
○	.....	○	praten
○	.....	○	smaakvermogen
○	.....	○	veranderingen in gewicht
○	.....	○	tintelingen in handen / voeten
○	.....	○	wassen / aankleden
○	.....	○	dagelijkse bezigheden
○	.....	○	moeheid
○	.....	○	conditie
○	.....	○	spierkracht

Andere problemen

.....

.....

Zou u met een deskundige willen praten over uw problemen?

○ ja ○ misschien ○ nee

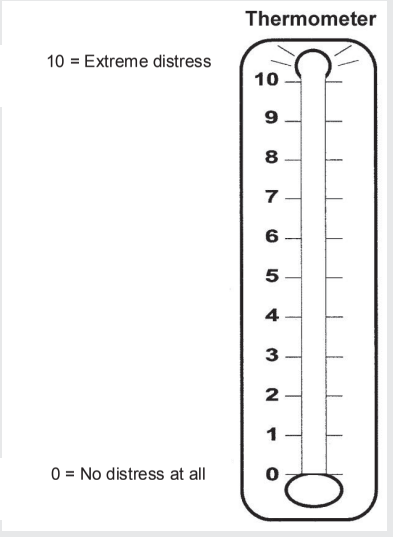
Zo ja, met wie?

○ verpleegkundige
○ diëtist
○ fysiotherapeut
○ maatschappelijk werker
○ geestelijk verzorger
○ psycholoog
○ lotgenoten
○ iemand anders

Distress thermometer and problem list

Date of today: ……. - ……. - ……. (day-month-year)

First, please circle the number on the thermometer that best describes how much distress you have been experiencing in the past week (including today) physically, emotionally, socially, practically and religiously.



Source NCCN, USA;
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Problem list

Second, please indicate by checking yes or no if any of the following has been a problem for you in the past week (including today). If yes, please rate from 1 (only a minor problem) to 10 (very serious problem) how much of a problem it has been.

Yes	if yes, how much	No	Practical problems
O	…….	O	child care
O	…….	O	housing
O	…….	O	housekeeping
O	…….	O	transportation
O	…….	O	work/school/study
O	…….	O	financial
O	…….	O	insurance
			Family / social problems
O	…….	O	dealing with partner
O	…….	O	dealing with children
O	…….	O	dealing with friends/family
			Emotional problems
O	…….	O	keeping emotions under control
O	…….	O	memory
O	…….	O	self confidence
O	…….	O	fears
O	…….	O	depression
O	…….	O	tension/nervousness
O	…….	O	loneliness
O	…….	O	concentration
O	…….	O	feelings of guilt
O	…….	O	loss of control
			Religious/spiritual concerns
O	…….	O	meaning of life
O	…….	O	trust in God / religion

Yes	if yes, how much	No	Physical problems
O	…….	O	appearance
O	…….	O	changes in urination
O	…….	O	constipation
O	…….	O	diarrhoea
O	…….	O	eating
O	…….	O	feeling swollen
O	…….	O	fever
O	…….	O	mouth sores
O	…….	O	nausea
O	…….	O	nose dry/congested
O	…….	O	pain
O	…….	O	sexual
O	…….	O	skin dry/itchy
O	…….	O	sleep
	…….	O	shortness of breath/breathing
O	…….	O	nausea
O	…….	O	speech/talking
O	…….	O	taste
O	…….	O	weight change
	…….	O	tingling in hands/feet
O	…….	O	bathing/ dressing
O	…….	O	daily activities
O	…….	O	fatigue
O	…….	O	out of shape/condition
O	…….	O	muscle strength

Other problems?

_____

_____

Would you like to talk with someone about your problems?

O yes O maybe O no

If yes, with whom?

O nurse
O dietician
O physiotherapist
O social worker
O pastoral worker
O psychologist
O fellow patients
O another, namely…

Dankwoord

DANKWOORD

Eindelijk is het zover: mijn proefschrift is af! Hoewel ik het traject niet altijd gemakkelijk vond, had ik deze 'PhD journey' niet willen missen. Vele leerzame en leuke ervaringen neem ik met me mee. Ervaringen die ik (ook) aan jullie te danken heb. Graag wil ik iedereen die aan mijn proefschrift heeft bijgedragen hierbij bedanken. Een aantal personen wil ik graag in het bijzonder noemen.

Mijn onderzoek zou onmogelijk zijn geweest zonder de deelname van de patiënten. De patiënten hebben de tijd en moeite genomen om vragenlijsten in te vullen, gesprekken te voeren, en om mailtjes en telefoontjes te beantwoorden. Individuele reacties zijn niet terug te vinden in dit proefschrift, maar zijn van grote waarde geweest voor het begrijpen van de resultaten: veel dank!

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